

World Journal of *Critical Care Medicine*

World J Crit Care Med 2015 February 4; 4(1): 1-104



Editorial Board

2011-2015

The *World Journal of Critical Care Medicine* Editorial Board consists of 246 members, representing a team of worldwide experts in critical care medicine. They are from 45 countries, including Argentina (2), Australia (8), Austria (2), Bangladesh (1), Belgium (3), Brazil (4), Canada (7), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (8), Germany (11), Greece (9), Hungary (1), India (10), Iran (2), Ireland (1), Israel (6), Italy (14), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (3), Singapore (1), Slovenia (1), South Africa (1), Spain (7), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (8), United States (72), and Uruguay (1).

EDITOR-IN-CHIEF

Yaseen Mohamed Arabi, *Riyadh*

GUEST EDITORIAL BOARD MEMBERS

Hsing I Chen, *Hualien*
Sheng-Hsien Chen, *Tainan*
Yih-Sharnng Chen, *Taipei*
Yung-Chang Chen, *Taipei*
Der-Yang Cho, *Taichung*
Cheng-Keng Chuang, *Taoyuan*
How-Ran Guo, *Tainan*
Bang-Gee Hsu, *Hualien*
Chien-Wei Hsu, *Kaohsiung*
Wen-Jinn Liaw, *Taipei*
Yan-Ren Lin, *Changhua*
Jiunn-Jye Sheu, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Eduardo Chuluyan, *Buenos Aires*
Adrian Angel Inchauspe, *Berazategui*



Australia

Zsolt J Balogh, *Newcastle*
Zoltan Huba Endre, *Sydney*
Nam Q Nguyen, *Adelaide*
Alistair D Nichol, *Melbourne*
Srinivas Rajagopala, *Adelaide*
Georg Marcus Schmolzer, *Melbourne*
Andrew Trevitt Slack, *Southport*
Ravindranath Tiruvoipati, *Frankston*



Austria

Lars-Peter Kamolz, *Vienna*
Sylvia Knapp, *Vienna*



Bangladesh

Saidur Rahman Mashreky, *Dhaka*



Belgium

Teresinha Leal, *Brussels*
Manu Malbrain, *Antwerp*
Jean-Louis Vincent, *Brussels*



Brazil

Luciano CP Azevedo, *São Paulo*
Patricia Rieken Macedo Rocco, *Rio de Janeiro*
Marcos Antonio Rossi, *São Paulo*
Renato Seligman, *Porto Alegre*



Canada

Douglas D Fraser, *London*
Pierre A Guertin, *Quebec*
Marc Jeschke, *Toronto*
Constantine J Karvellas, *Edmonton*
Wolfgang Michael Kuebler, *Toronto*
Mingyao Liu, *Toronto*
Xi Yang, *Manitoba*



China

Xiang-Dong Chen, *Chengdu*

Xu-Lin Chen, *Hefei*
Wong Tak Chuen, *Hong Kong*
Ming-Xu Da, *Gansu*
Huang-Xian Ju, *Nanjing*
Ting-Bo Liang, *Hangzhou*
Peng-Lin Ma, *Beijing*
Chung-Wah David Siu, *Hong Kong*
Yong-Ming Yao, *Beijing*
Jia-Ping Zhang, *Chongqing*
Wei-Dong Zhou, *Beijing*



Croatia

Alan Sustic, *Rijeka*



Cuba

Jesús Pérez-Nellar, *La Habana*



Denmark

Dan Stieper Karbing, *Aalborg*



Egypt

Ibrahim Abouomira, *Cairo*
Hanan Ibrahim, *Cairo*
Amr M Moghazy, *Alexandria*
Ayman A Yousef, *Tanta*



Finland

Asko Armas Riutta, *Tampere*

**France**

Jean-Marc Cavaillon, *Paris*
 Jean-Michel Constantin, *Clermont-Ferrand*
 Marc Leone, *Marseille*
 Bruno Mégarbane, *Paris*
 Saad Nseir, *Lille*
 Nicolas Terzi, *Caen*
 Jean-François Timsit, *La Tronche Cedex*
 Benoit Vallet, *Lille*

**Germany**

Hendrik Bracht, *Ulm*
 Michael Czaplik, *Aachen*
 Gerrit Grieb, *Aachen*
 Tobias Keck, *Freiburg*
 Philipp Kobbe, *Aachen*
 Alexander Koch, *Aachen*
 Marc Maegele, *Cologne*
 Norbert Pallua, *Aachen*
 Andrzej Antoni Piatkowski, *Aachen*
 Armin Rudolf Sablotzki, *Leipzig*
 Kai D Zacharowski, *Frankfurt am Main*

**Greece**

Ioanna Dimopoulou, *Athens*
 Dimitrios Karakitsos, *Athens*
 Petros Kopterides, *Athens*
 Gregory Kouraklis, *Athens*
 Athanasios D Marinis, *Athens*
 George Nakos, *Ioannina*
 Papaioannou E Vasilios, *Alexandroupolis*
 Theodoros Xanthos, *Athens*
 Spyros G Zakyntinos, *Athens*

**Hungary**

Zoltan Rakonczay, *Szeged*

**India**

Rachna Agarwal, *Delhi*
 Ritesh Agarwal, *Chandigarh*
 Mohammad Farooq Butt, *Srinagar*
 Mohan Gurjar, *Lucknow*
 Deven Juneja, *New Delhi*
 Farhad N Kapadia, *Mumbai*
 Vikram Kate, *Pondicherry*
 Pramod Kumar, *Manipal*
 Ritesh G Menezes, *Mangalore*
 Medha Mohta, *Delhi*

**Iran**

Hemmat Maghsoudi, *Tabriz*
 Homayoun Sadeghi-Bazargani, *Tabriz*

**Ireland**

Sanjay H Chotirmall, *Dublin*

**Israel**

Alexander Becker, *Kefar Tavor*
 Yoram Kluger, *Haifa*
 Yona Kosashvili, *Zerrifin*
 Kobi Peleg, *Tel Aviv*
 Ilan Sela, *Rehovot*
 Pierre Singer, *Tel Aviv*

**Italy**

Giacomo Bellani, *Monza*
 Giovanni Camussi, *Torino*
 Anselmo Caricato, *Rome*
 Piero Ceriana, *Pavia*
 Antonio Chiaretti, *Rome*
 Davide Chiumello, *Milano*
 Alfredo Conti, *Messina*
 Paolo Cotogni, *Torino*
 Daniele M De Luca, *Rome*
 Vincenzo De Santis, *Rome*
 Luca La Colla, *Parma*
 Giovanni Landoni, *Milano*
 Raffaele Scala, *Lucca*
 Giovanni Vento, *Rome*

**Japan**

Keishiro Aoyagi, *Kurume*
 Satoshi Hagiwara, *Yufu*
 Yuichi Hattori, *Toyama*
 Hideo Inaba, *Kanazawa*
 Eisuke Kagawa, *Hiroshima*
 Chieko Mitaka, *Tokyo*

**Jordan**

Feras Ibrahim Hawari, *Amman*

**Mexico**

Silvio A Ñamendys-Silva, *Mexico City*

**Morocco**

Redouane Abouqal, *Rabat*

**Netherlands**

WA Buurman, *Maastricht*
 Martin CJ Kneyber, *Groningen*
 Patrick Schober, *Amsterdam*
 Arie Barend Van Vugt, *Enschede*

**New Zealand**

Sultan Zayed Al-Shaqsi, *Dunedin*
 Arman Adam Kahokehr, *Whangarei*
 John William Pickering, *Christchurch*

**Norway**

Ulf R Dahle, *Oslo*

**Poland**

Maciej Owecki, *Poznań*

**Portugal**

Ernestina Rodrigues Gomes, *Porto*
 Cristina Granja, *Porto*
 José António Lopes, *Lisbon*
 Pedro M Póvoa, *Lisbon*

**Russia**

Konstantin A Popugaev, *Moscow*

**Saudi Arabia**

Imran Khalid, *Jeddah*
 Mohamed Taifour Suliman, *Tabuk*

**Singapore**

Devanand Anantham, *Singapore*

**Slovenia**

Štefek Grmec, *Maribor*

**South Africa**

DL Clarke, *Pietermaritzburg*

**Spain**

Juan Carlos Montejo González, *Madrid*
 David Jimenez, *Madrid*
 Juan Antonio Llompарт-Pou, *Palma*
 Antonio Torres Mart, *Barcelona*
 Enrique Ariel Piacentini, *Barcelona*
 Alonso Mateos Rodriguez, *Madrid*
 R Rodríguez-Roisin, *Barcelona*

**Sweden**

Mihai Oltean, *Gothenburg*

**Switzerland**

Dieter Cadosch, *Zurich*
 Mihael Potocki, *Basel*
 John Friedrich Stover, *Zurich*

**Thailand**

Viroj Wiwanitkit, *Bangkok*

**Tunisia**

Mabrouk Bahloul, *Sfax*

**Turkey**

Yusuf Kenan Coban, *Malatya*
Bensu Karahalil, *Ankara*
Ali Nayci, *Mersin*

**United Kingdom**

Sammy Al-Benna, *Nottingham*
Giles N Cattermole, *London*
Frantisek Duska, *Nottingham*
James Nicholas Fullerton, *London*
Christina Jones, *Prescot*
Sameer Khan, *Middlesbrough*
George Ntoumenopoulos, *London*
Cecilia O'Kane, *Belfast*

**United States**

Edward Abraham, *Winston-Salem*
Bernard R Bendok, *Chicago*
Michael Blaivas, *Atlanta*

Charles D Boucek, *Pittsburgh*
Marcia Leigh Brackbill, *Winchester*
Ronald A Bronicki, *Houston*
Robert C Cantu, *Concord*
Marylou Cardenas-Turanzas, *Houston*
Archana Chatterjee, *Omaha*
Paul A Checchia, *St. Louis*
Rubin Issam Cohen, *New Hyde Park*
Stephen Cohn, *San Antonio*
Donald Edward Craven, *Burlington*
Ruy J Cruz Jr, *Pittsburgh*
Francis C Dane, *Roanoke*
Marc de Moya, *Boston*
Steven M Donn, *Ann Arbor*
Christopher P Farrell, *Wynnewood*
Marco Fernández, *Nashville*
Kevin Foster, *Phoenix*
Barry D Fuchs, *Philadelphia*
Richard P Gonzalez, *Mobile*
Kenneth W Gow, *Seattle*
Alan H Hall, *Laramie*
Jijo John, *Oklahoma City*
Lewis J Kaplan, *New Haven*
Jason N Katz, *Chapel Hill*
Salah Georges Keyrouz, *Little Rock*
Deborah A Kuhls, *Las Vegas*
Gregory Luke Larkin, *New Haven*
Christos Lazaridis, *Charleston*
James Anthony Lin, *Los Angeles*
Yahia M Lodi, *Syracuse*
Roger M Loria, *Richmond*
Aigang Lu, *Cincinnati*
Rudolf Lucas, *Augusta*
O John Ma, *Portland*
Robert T Mallet, *Fort Worth*
William T McGee, *Springfield*
Mark G McKenney, *Miami*

Michael Moussouttas, *Philadelphia*
Oliver Hans-Josef Muensterer, *Birmingham*
Rahul Nanchal, *Milwaukee*
Michael Steven Niederman, *Mineola*
Gary Frank Nieman, *Syracuse*
James Martin O'Brien, *Columbus*
Martin Oudega, *Pittsburgh*
Catherine Mobley Preissig, *Duluth*
Virginia Prendergast, *Phoenix*
Ramesh Raghupathi, *Philadelphia*
Miren Ava Schinco, *Jacksonville*
Carl Ivan Schulman, *Miami*
L Keith Scott, *Shreveport*
Kevin Navin Sheth, *Baltimore*
Jenni Short, *Salina*
Ronald Fong Sing, *Charlotte*
Philip Charles Spinella, *St. Louis*
Robert M Starke, *Charlottesville*
Stanislaw Peter A Stawicki, *Columbus*
David Christopher Stockwell, *Washington*
Stanislav Svetlov, *Gainesville*
Maged A Tanios, *Long Beach*
Neal James Thomas, *Hershey*
Nancy Moon Tofil, *Birmingham*
Balagangadhar R Totapally, *Miami*
Steven Nicholas Vaslef, *Durham*
Joseph Clark Watson, *Falls Church*
John Stephen Wilgis, *Orlando*
David Conrad Willms, *San Diego*
Haodong Xu, *Rochester*
Xiao-Ming Xu, *Indianapolis*
Midori Anne Yenari, *San Francisco*

**Uruguay**

William Manzanares, *Montevideo*

Contents

Quarterly Volume 4 Number 1 February 4, 2015

REVIEW

- 1 Modeling cardiac arrest and resuscitation in the domestic pig
Cherry BH, Nguyen AQ, Hollrah RA, Olivencia-Yurvati AH, Mallet RT
- 13 Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us
Zhang YZ, Singh S
- 29 Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014
Michiels JJ, Michiels JM, Moosdorff W, Lao M, Maasland H, Palareti G
- 40 Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy
Yasuda H, Matsuo Y, Sato Y, Ozawa S, Ishigooka S, Yamashita M, Yamamoto H, Itoh F

MINIREVIEWS

- 47 Noninvasive ventilation in trauma
Karcz MK, Papadakis PJ
- 55 Checklist for early recognition and treatment of acute illness: International collaboration to improve critical care practice
Vukoja M, Kashyap R, Gavrilovic S, Dong Y, Kilickaya O, Gajic O
- 62 Has Stewart approach improved our ability to diagnose acid-base disorders in critically ill patients?
Masevicius FD, Dubin A

ORIGINAL ARTICLE

Observational Study

- 71 Serum bicarbonate may independently predict acute kidney injury in critically ill patients: An observational study
Gujadhur A, Tiruvoipati R, Cole E, Malouf S, Ansari ES, Wong K

SYSTEMATIC REVIEWS

- 77 Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: A systematic review
Field-Ridley A, Sethi V, Murthi S, Nandalike K, Li STT
- 89 Thoracic epidural anesthesia: Effects on splanchnic circulation and implications in Anesthesia and Intensive care
Siniscalchi A, Gamberini L, Laici C, Bardi T, Faenza S

Contents

World Journal of Critical Care Medicine
Volume 4 Number 1 February 4, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Armin Rudolf Sablotzki, Professor, Klinikum St. Georg gGmbH, Clinics of Anesthesiology, Critical Care and Pain Therapy, Delitzscher Str. 141, 04129 Leipzig, Germany

AIM AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, and application of bronchofiberscopy in critically ill patients.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Critical Care Medicine is now indexed in PubMed Central, PubMed, Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Yue-Li Tian*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Yaseen Mohamed Arabi, MD, FCCP, FCCM, Associate Professor, Chairman, Intensive Care Department, King Saud Bin Abdulaziz University, Medical Director, Respiratory Services, King Abdulaziz Medical City, National Guard Hospital, Riyadh, PO Box 22490, Riyadh 11426, Saudi Arabia

Derek S Wheeler, MD, FAAP, FCCP, FCCM, Associate Professor, Associate Patient Safety Officer, Medical Director, Pediatric Intensive Care Unit, Division of Critical Care Medicine, James M. Anderson Center for Health Systems Excellence, The Center for Simulation and Research, Co-Director, The Center

for Acute Care Nephrology, Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>

<http://www.wjnet.com>

PUBLICATION DATE

February 4, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Modeling cardiac arrest and resuscitation in the domestic pig

Brandon H Cherry, Anh Q Nguyen, Roger A Hollrah, Albert H Olivencia-Yurvati, Robert T Mallet

Brandon H Cherry, Anh Q Nguyen, Roger A Hollrah, Albert H Olivencia-Yurvati, Robert T Mallet, Department of Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, TX 76107, United States
 Brandon H Cherry, Anh Q Nguyen, Roger A Hollrah, Robert T Mallet, Department of Integrative Physiology and Anatomy Research Institute, University of North Texas Health Science Center, Fort Worth, TX 76107, United States
 Brandon H Cherry, Robert T Mallet, Institute of Aging and Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, TX 76107, United States
 Albert H Olivencia-Yurvati, Department of Surgery Research Institute, University of North Texas Health Science Center, Fort Worth, TX 76107, United States

Author contributions: Cherry BH, Nguyen AQ, Hollrah RA and Mallet RT researched the literature, wrote and edited the manuscript and prepared the figures; Olivencia-Yurvati AH reviewed and edited the manuscript for clinical accuracy.

Supported by Grants from The United States National Institute of Neurological Disorders and Stroke, No. R01 NS076975-03; a predoctoral fellowship from the United States National Institute of Aging, Training in the Neurobiology of Aging, No. T31 AG020494; and a predoctoral fellowship from the University of North Texas Health Science Center's Physician Scientist Program.
Conflict-of-interest: The authors declare that they have no competing interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Robert T Mallet, PhD, Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, United States. robert.mallet@unthsc.edu
 Telephone: +1-817-7352260
 Fax: +1-817-7355084

Received: August 8, 2014

Peer-review started: August 8, 2014

First decision: October 31, 2014

Revised: November 3, 2014

Accepted: November 27, 2014

Article in press: November 27, 2014

Published online: February 4, 2015

Abstract

Cardiac arrest remains a leading cause of death and permanent disability worldwide. Although many victims are initially resuscitated, they often succumb to the extensive ischemia-reperfusion injury inflicted on the internal organs, especially the brain. Cardiac arrest initiates a complex cellular injury cascade encompassing reactive oxygen and nitrogen species, Ca^{2+} overload, ATP depletion, pro- and anti-apoptotic proteins, mitochondrial dysfunction, and neuronal glutamate excitotoxicity, which injures and kills cells, compromises function of internal organs and ignites a destructive systemic inflammatory response. The sheer complexity and scope of this cascade challenges the development of experimental models of and effective treatments for cardiac arrest. Many experimental animal preparations have been developed to decipher the mechanisms of damage to vital internal organs following cardiac arrest and cardiopulmonary resuscitation (CPR), and to develop treatments to interrupt the lethal injury cascades. Porcine models of cardiac arrest and resuscitation offer several important advantages over other species, and outcomes in this large animal are readily translated to the clinical setting. This review summarizes porcine cardiac arrest-CPR models reported in the literature, describes clinically relevant phenomena observed during cardiac arrest and resuscitation in pigs, and discusses numerous methodological considerations in modeling cardiac arrest/CPR. Collectively, published reports show the domestic pig to be a suitable large animal model of cardiac arrest which is responsive to CPR, defibrillatory countershocks and medications, and yields extensive information to foster advances in clinical treatment of cardiac arrest.

Key words: Acidemia; Asphyxia; Cardiopulmonary

resuscitation; Countershocks; Hyperoxia; Vasopressin; Ventricular fibrillation

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Cardiac arrest remains a leading cause of death worldwide, despite tremendous improvements in emergency medical care and increased public delivery of bystander cardiopulmonary resuscitation (CPR). But progress is being achieved, thanks to the joint efforts of biomedical scientists, physicians and emergency medical personnel to translate laboratory discoveries to the ambulance and hospital. The domestic pig has proven to be a superb preclinical model of cardiac arrest, yielding a wealth of mechanistic insights and practical strategies to refine the delivery of CPR and to test promising treatments. This review examines pivotal factors in modeling cardiac arrest and CPR in the pig.

Cherry BH, Nguyen AQ, Hollrah RA, Olivencia-Yurvati AH, Mallet RT. Modeling cardiac arrest and resuscitation in the domestic pig. *World J Crit Care Med* 2015; 4(1): 1-12 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/1.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.1>

INTRODUCTION

Prior to 1960 cardiac resuscitation was administered by direct cardiac massage following thoracotomy. Based on animal experimentation a method of external cardiac massage administered by rapid, forceful compressions and passive recoil of the sternum was developed by Kouwenhoven *et al*^[1]. Although over fifty years have passed since the inception of closed chest cardiac massage, and despite many refinements of this approach in the intervening decades, cardiac arrest remains a leading cause of death and persistent disability worldwide. All too often, victims who are initially resuscitated later succumb to extensive ischemia-reperfusion injury to their vital organs, especially the brain^[2-5]. Further, many of the 10% of cardiac arrest patients who survive to hospital discharge experience persistent neurocognitive impairment which profoundly impacts their quality of life^[3,6].

Although public health data and anecdotal evidence inform the refinement of cardiopulmonary resuscitation (CPR) protocols^[7], knowledge of the complex mechanisms of internal organ damage, essential to foster development of effective pharmacological interventions, is incomplete. In the brain, ATP depletion, intracellular Ca²⁺ overload, excessive formation of reactive oxygen and nitrogen derivatives, inflammation and glutamate-induced excitotoxicity conspire to kill neurons and other cells and disrupt the blood-brain barrier. Currently

there are no clinically effective pharmacological treatments to protect the brain during cardiac arrest and CPR^[2], and therapeutic hypothermia is the only approved treatment in the United States^[8]. Reliable preclinical models of cardiac arrest and resuscitation are essential to decipher the injury mechanisms and develop treatments to increase survival and improve quality of life after cardiac arrest.

Ischemia-reperfusion damage in the central nervous system is the result of a multifaceted injury cascade^[9,10]. The structural complexity of the brain, which consists of integrated networks of different cell types including neurons, astrocytes, oligodendrocytes, microglia and vascular endothelium, presents fundamental challenges to developing neuroprotective treatments. The brain contains many functional regions which differ in their vulnerabilities to ischemia-reperfusion injury. Potential pharmacotherapeutic agents must first traverse the blood brain barrier, a significant permeability impediment to all but small, non-polar compounds, and act on multiple injury mechanisms, without producing untoward side effects.

Sophisticated animal models are required to model the composite structure and integrated function of the central nervous system and to evaluate the benefits and potential side effects of prospective treatments for ischemia and other brain disorders. Extensive research has established the domestic pig as an excellent animal model to study the impact of cardiac arrest, resuscitation, and therapeutic interventions on the brain and other internal organs. An impressive variety of swine cardiac arrest models are reported in the literature. By examining the features that distinguish these models, this article aims to assist the reader in evaluating the literature and in designing porcine cardiac arrest models appropriate to address specific research objectives.

ATTRIBUTES OF SWINE FOR MODELING CARDIAC ARREST AND RESUSCITATION

Several attributes make the domestic pig an ideal model for cardiac arrest research^[11,12]: (1) a large mammal, the pig accommodates extensive instrumentation for blood sampling, monitoring of intravascular and intracardiac pressures, electrocardiography and intravenous administration of medications and experimental treatments; (2) pigs tolerate invasive surgical procedures and rapidly regain consciousness post-anesthesia; (3) resting heart rate, blood pressure, and serum chemistries of pigs and humans are very similar^[13-15]; (4) pigs have sufficient blood volume to permit collection of multiple arterial and venous samples for analyses of blood gases and serum chemistry; (5) neurological examinations have been developed to evaluate neurobehavioral function

Table 1 Details of representative cardiac arrest protocols in pigs

Ref.	Lurie <i>et al</i> ^[93] , 2002	Mayr <i>et al</i> ^[38] , 2004	Tang <i>et al</i> ^[25] , 2006	Li <i>et al</i> ^[94] , 2008	Indik <i>et al</i> ^[95] , 2009	Hang <i>et al</i> ^[96] , 2014
Pre-anesthetic, induction anesthetic	Ketamine 20 mg/kg <i>im</i> Propofol 2.3 mg/kg <i>iv</i>	Ketamine 20 mg/kg <i>im</i> Propofol 1-2 mg/kg <i>iv</i> Piritramide 30 mg <i>iv</i>	Ketamine 20 mg/kg <i>im</i> Pentobarbital 30 mg/kg <i>iv</i>	Ketamine 20 mg/kg <i>im</i> Pentobarbital 30 mg/kg <i>iv</i>	5% isoflurane	Ketamine 15 mg/kg <i>im</i> Midazolam 0.5 mg/kg <i>im</i> Atropine 0.05 mg/kg <i>im</i> Propofol 1 mg/kg <i>iv</i>
Maintenance anesthesia	Propofol 10 mg/kg per hour <i>iv</i>	Isoflurane (1%-2%) in 65% nitrous oxide	Pentobarbital 8 mg/kg per hour <i>iv</i>	Pentobarbital 8 mg/kg per hour <i>iv</i>	1.5%-3% isoflurane	Propofol 9 mg/kg per hour <i>iv</i> Fentanyl 1 µg/kg per hour <i>iv</i>
Method of arrest	Electrical: 60 Hz, 140-160 V	Pharmacological: 5 mg/kg bupivacaine	Electrical: 1-2 mA	LAD balloon occluder	Steel plug in LAD	Asphyxiation: endotracheal clamping
Pre-CPR arrest	6 min	6 min	7 min	5 min	8 min	8 min
Precordial compressions (% of chest diameter)	Mechanical: 80/min (25%)	Manual: 100/min	Mechanical: 100/min (25%)	Mechanical: 100/min (Group 1 25%, Group 2 17.5%)	Manual: 100/ min (c. 33%)	Manual: 100/min (c. 33%)
CPR duration	6 min	2 min	1 min	3 min	2 min	4 min
Ventilation during CPR?	F _{IO2} = 1.0; 5:1 compression: ventilation	F _{IO2} = 1.0	F _{IO2} = 1.0; 15:2 compression: ventilation	F _{IO2} = 1.0; 15:2 compression: ventilation	None	F _{IO2} = 1.0; 12 cycles/ min; 10 mL/kg per cycle
Countershocks CPR between countershocks	1-3 x 200 J 90 s	3, 4, 6 J/kg None	150-360 J 1 min/shock	150 J 3 min	150 J 2 min	4 J/kg 2 min
Vasopressors to enhance CPR	EPI 0.045 mg/kg	AVP 0.4 or 0.8 U/kg ± EPI 45 or 200 µg/kg	None	None	EPI 0.02 µg/kg; 1-3 doses	EPI 0.02 µg/kg
Definition of ROSC	Systolic BP > 70 mmHg	Systolic BP ≥ 80 mmHg for ≥ 5 min	Mean aortic BP > 60 mmHg for ≥ 5 min	Mean aortic BP ≥ 60 mmHg for ≥ 5 min	Systolic BP > 50 mmHg for > 1 min	Systolic BP > 50 mmHg for > 10 min
ROSC duration	24 h	1 h	3 d	72 h	24 h	6 h
Pigs completing protocol	11/20	Placebo: 0/7; AVP: 5/7; EPI: 4/7; AVP + EPI: 7/7	36/44	Group 1: 6/6 Group 2: 0/6	11/15	ROSC: 8/16; Complete protocol: 3/16

AVP: Vasopressin; BP: Systemic arterial blood pressure; CPR: Cardiopulmonary resuscitation; EPI: Epinephrine; LAD: Left anterior descending coronary artery; ROSC: Recovery of spontaneous circulation.

in pigs^[16,17]; (6) the pig's large chest accommodates forceful precordial chest compressions and application of transthoracic defibrillatory countershocks of electrical energies similar to those used clinically; and (7) pigs have the largest brains among the commonly studied laboratory animals, which provides ample tissue for extensive biochemical and histological analyses of specific brain subregions. Porcine models are especially well-suited to study cardiac arrest and CPR, because they are easily tailored to address specific research objectives.

FACTORS TO CONSIDER WHEN MODELING CARDIAC ARREST AND RESUSCITATION IN PIGS

The pathophysiological complexities of sudden cardiac death and cardiopulmonary resuscitation challenge the development of animal models that accurately replicate the clinical situation. The primary

factors in developing suitable animal models are the study end points and objectives. However, the myriad variables in model design and experimental protocol, which mirror the complexity of cardiac arrest and its treatment, challenge the direct comparison of results obtained in different studies. This section summarizes several factors that must be considered in developing and reporting cardiac arrest-resuscitation protocols in pigs, including the anesthetic regimen, method of inducing ventricular fibrillation, the depth, frequency and duration of chest compressions, whether or not to ventilate during resuscitation and the fraction of inspired O₂ (F_{IO2}), the pattern and intensity of defibrillatory countershocks, the criteria taken to indicate recovery of spontaneous circulation (ROSC), the use of inotropic and/or vasoconstrictor support during ROSC, and strategies to correct post-arrest systemic acidemia. With multiple options for each component, it is critical that cardiac arrest-resuscitation protocols be designed carefully to address the study's specific

objectives. Table 1 summarizes and compares key features of representative cardiac arrest-resuscitation protocols in domestic swine.

Induction and maintenance of anesthesia

Invasive surgical procedures and ethical constraints require the induction and maintenance of an appropriate anesthetic plane. Anesthetics are infused intravenously or, in the case of volatile anesthetics, inhaled. The temporary or persistent effects of the anesthetic on study endpoints, *e.g.*, cardiac function, cell death, inflammation or neurobehavioral recovery must be taken into account. For example, the cardiodepressant effects of some volatile anesthetics, *e.g.*, halothane and isoflurane may produce hypotension^[18-21], yet these anesthetics also exert cardioprotection^[22,23]; thus, the anesthetic plane must be controlled carefully. Signs of inadequate anesthesia include increased jaw tension, limb withdrawal when the soft tissue between the hooves is pinched, wink reflex in response to delicate contact of the ocular canthus, spontaneous limb movements, and/or unexpected increases in heart rate and systemic arterial pressure.

Methods of inducing cardiac arrest

The major causes of clinical cardiac arrest are asphyxiation, electric shock and, most commonly, coronary artery occlusion and reperfusion. There are different methods of inducing cardiac arrest which model these clinical situations. The first and most common method of inducing ventricular fibrillation is the application of electrical current to the epicardium or, in closed-chest preparations, the left or right ventricular endocardium. Typically, a pacing wire is introduced into the external jugular vein and advanced into the right ventricle (Figure 1)^[24-27]. While the wire is in contact with the right ventricular endocardium, a rapid train of impulses is transmitted which, within seconds, initiates ventricular fibrillation. The characteristic "torsades de pointes" pattern on electrocardiogram (*cf.* Figure 2), monophasic decline in aortic pressure and the absence of an arterial pulse confirm ventricular fibrillation. Aside from modeling electrocution-induced cardiac arrest, an important advantage of this method is the well-defined and reproducible time of ventricular fibrillation onset. Electrical induction of ventricular fibrillation does not impart substantial myocardial injury, which is advantageous if the study is examining other internal organs in which persistent cardiac insufficiency might be a confounding factor.

Myocardial ischemia imposed by coronary stenosis or occlusion is the leading cause of cardiac arrest. Porcine models of ischemia-induced ventricular fibrillation are available that accurately reproduce the pathophysiology of cardiac arrest. Porcine

myocardium lacks significant coronary collateral vessels, so the ischemia imposed by occlusion of a major coronary artery, *e.g.*, the left anterior descending coronary artery, is sufficiently severe to initiate ventricular fibrillation within several minutes of occlusion. Coronary occlusions may be imposed by introducing a balloon occluder (one used for percutaneous transluminal coronary angioplasty) and routing it, with the aid of fluoroscopy^[28], into the target vessel before inflating it. An alternative approach is the use of an ameroid occluder around a coronary artery; however, this procedure requires invasive thoracotomy and pericardiotomy to permit placement of the occluder, necessitating post-surgical recovery of the animal before the cardiac arrest experiment. In either case, occlusion may be confirmed by arteriography^[28,29]. A third method is advancement of a Teflon^[30] or steel^[31] plug into the coronary artery. Ventricular fibrillation typically ensues within 5-10 min of coronary occlusion^[29,31]. The coronary occlusion may be released, *e.g.*, release of the balloon or ameroid occluder upon defibrillation^[28,29] or the intracoronary plug may be permanently installed, resulting in a myocardial infarct^[30]. Because the onset of cardiac arrest is delayed to a variable extent while the artery is occluded, the severity of myocardial injury may vary considerably among experiments. The number and intensity of the countershocks required to restore sinus rhythm is greater in porcine models of ischemically-induced vs electrically-induced arrest, as is the incidence of post-resuscitation ventricular premature beats and recurrence of ventricular fibrillation^[29,32,33]. Nevertheless, ischemia-induced cardiac arrest replicates the most common cause of cardiac arrest, affording ready translation of results to clinical settings.

Asphyxiation is the second most common cause of cardiac arrest and the leading cause in children. A facile method of producing asphyxia in anesthetized swine is to block the endotracheal tube while monitoring the electrocardiogram and arterial blood pressure^[34-36]. Hypoxemia and hypercapnia progressively intensify until cardiac arrest ensues, typically within 10-15 min after blocking ventilation^[37]. The principal advantages of asphyxia are its accurate modeling of a major cause of pediatric cardiac arrest and mortality, including the changes in blood gases and pH, and the noninvasive approach which obviates the introduction of pacing wires or occluders into the vasculature. Depending on the study endpoints and objectives, disadvantages may include the changes in blood gas chemistry^[37] and the variable duration of asphyxiation before ventricular fibrillation, which imposes hypoxemia on the brain and other internal organs even before onset of cardiac arrest.

High dosages of certain chemicals, *e.g.*, bupiva-

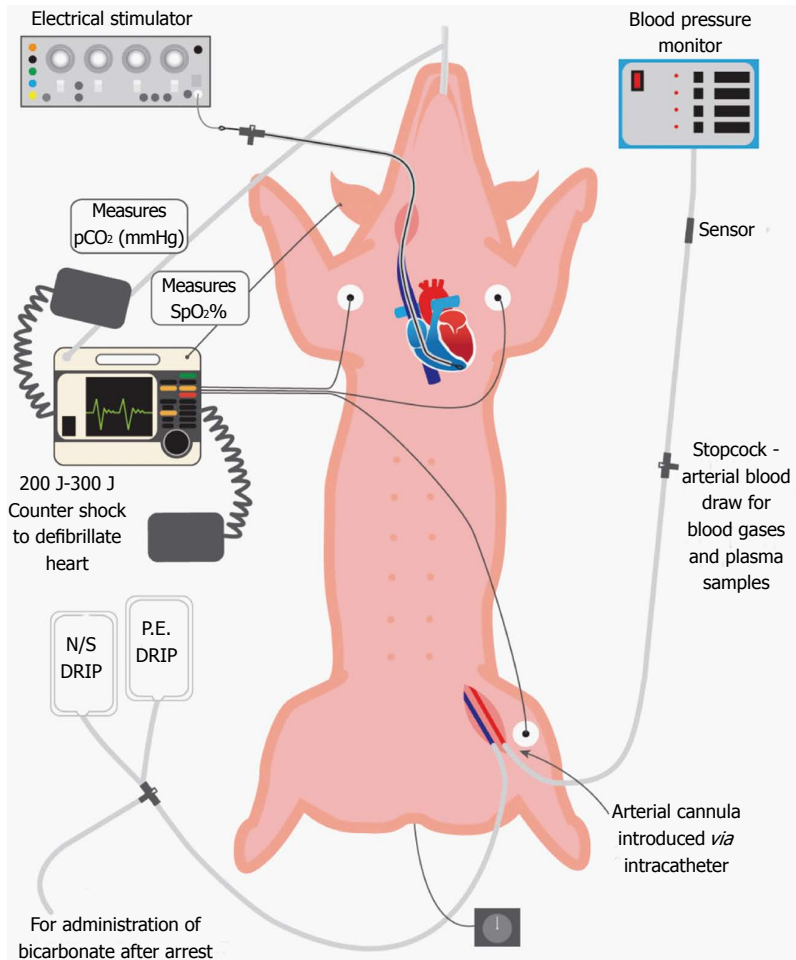


Figure 1 Porcine preparation for cardiac arrest-cardiopulmonary resuscitation studies. The pig is placed in supine recumbency and mechanically ventilated via an endotracheal tube, through which isoflurane anesthesia is administered. Hemodynamic function is monitored by a femoral arterial catheter connected to a pressure transducer, and electrocardiographic activity is monitored by standard limb lead II electrocardiogram. Cardiac arrest is induced by a train of electrical impulses conducted by an intrajugular pacing wire from an electrical stimulator to the right ventricular endocardium. Body temperature is measured with a rectal probe, and end-tidal pCO₂ by a sensor placed in the endotracheal tube. Defibrillatory countershocks (200-300 J) are administered with external paddles. Intravenous treatments include normal saline (N/S), phenylephrine (PE), sodium bicarbonate and experimental resuscitative fluids. spO₂: Percentage oxyhemoglobin saturation.

caine^[38], may be injected into the right atrium to arrest the heart, modeling cardiac arrest secondary to drug overdose. In such models the potential systemic side effects of the chemicals must be taken into account.

Duration of pre-CPR arrest

The duration of pre-intervention arrest is crucial; as this interval is prolonged, cardioversion, survival and good neurological recovery become progressively less achievable. The three-phase model of cardiac arrest^[39] subdivides the pre-intervention period into three phases. The first 4-5 min constitute the electrical phase, during which countershocks are likely to achieve cardioversion even without pre-shock CPR. During the next 5-10 min, the circulatory phase, interventions to effect circulation, *e.g.*, chest compressions, are essential to ensure countershocks produce cardioversion. After 10-15 min arrest, the victim enters the *metabolic phase*, in which increasingly intense metabolic derangements result in protracted or permanent organ damage and severe neurological impairment even if cardioversion is achieved. If the study requires a high survival rate, the period of pre-intervention cardiac arrest may be limited to assure a high rate of defibrillation and ROSC.

Cardiopulmonary resuscitation: force, frequency and duration

By affording modest delivery of O₂ and metabolic fuels to the myocardium, precordial compressions may support enough myocardial ATP production to sustain ion transport and repolarize cardiomyocytes, enabling defibrillatory countershocks to restore spontaneous electrical rhythm. Indeed, in a canine cardiac arrest model, effective CPR afforded partial recovery of myocardial Gibbs free energy of ATP hydrolysis^[40], the immediate energy source for cardiac electromechanical activity. Cardiopulmonary resuscitation protocols are readily customized to address the study end points. The frequency and depth of precordial compressions can profoundly influence outcome^[41-44]. In some studies, CPR is administered by a pneumatic, piston-driven device (*e.g.*, Thumper®), which can be adjusted to deliver forceful compressions at a predetermined frequency and depth, ensuring consistency of frequency and depth of compressions across experiments^[25]. Alternatively, precordial compressions can be administered manually, modeling the CPR given by a bystander responding to an out-of-hospital cardiac arrest. Current American Heart Association guidelines^[45] recommend manual mid-sternal chest compressions be sufficiently forceful to compress the

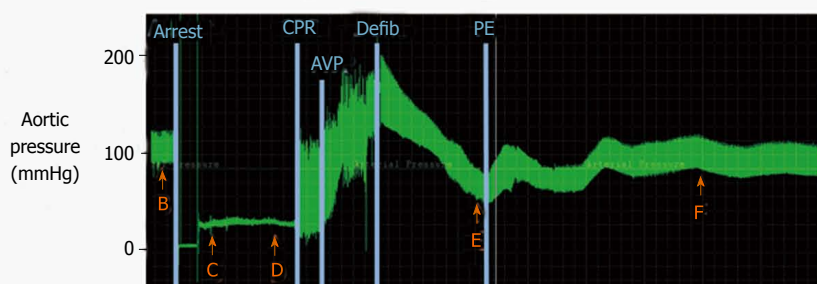
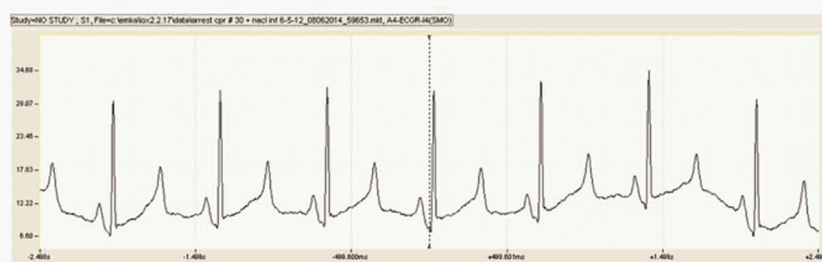
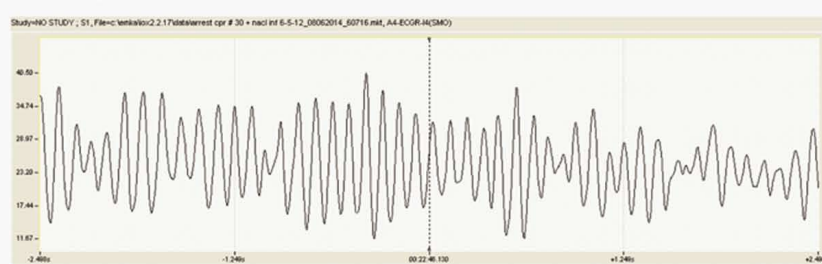
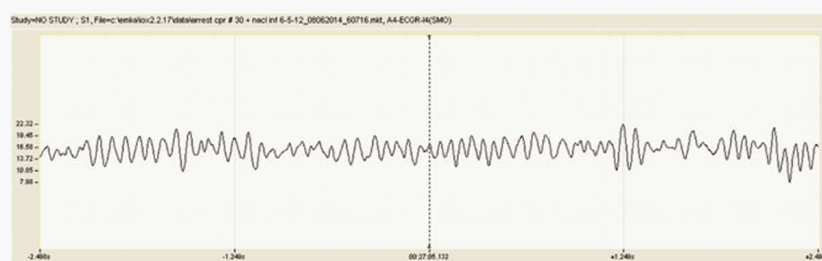
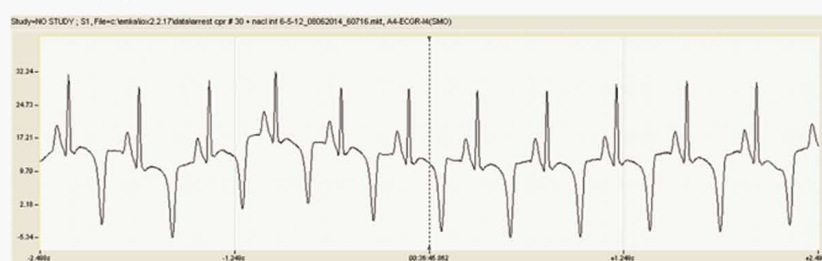
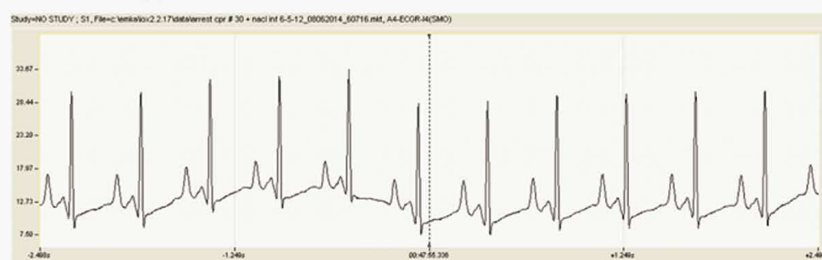
A: Aortic pressure tracing**B:** Pre-arrest baseline**C:** 1 min VF**D:** 5 min VF**E:** 5 min ROSC**F:** 15 min ROSC

Figure 2 Aortic pressures and lead II electrocardiogram during cardiac arrest, cardiopulmonary resuscitation and recovery of spontaneous circulation. A: Phasic aortic pressure tracing during the period from pre-arrest baseline to 20 min ROSC. Lettered arrows indicate times at which the electrocardiograms shown in panels B-F were obtained. Vertical lines indicate: (1) induction of ventricular fibrillation cardiac arrest; (2) commencement of precordial compressions (CPR); (3) injection of vasopressin (AVP); (4) defibrillation (Defib) by 200 J countershock; and (5) initiation of intravenous phenylephrine (PE; c. 2 µg/kg per minute) to stabilize systemic arterial pressure during ROSC. Mechanical ventilation was suspended during cardiac arrest and CPR. Panels B-F show 5 s electrocardiographic recordings. CPR: Cardiopulmonary resuscitation; ROSC: Recovery of spontaneous circulation; AVP: Vasopressin; PE: Phenylephrine.

chest by one-fourth of its antero-posterior diameter, followed by release and recoil, at a rate of 100 cycles/min.

The duration of CPR before defibrillatory countershocks is an important factor. Longer intervals model the protracted CPR given by bystanders before arrival of the ambulance team, but also lower the likelihood of post-arrest survival with good neurological outcome. Another important consideration is whether or not the animal will be ventilated during CPR and, if so, at what compression: ventilation ratio and FIO₂. Extensive clinical evidence demonstrates that assisted ventilation during CPR following witnessed cardiac arrest offers little or no neurological or survival benefit^[26,46-49]. In accordance with current recommendations for bystander CPR^[50], mechanical ventilation may be suspended for the duration of cardiac arrest and CPR, then resumed after confirming defibrillation to a productive sinus rhythm.

A systemic vasoconstrictor may be administered intravenously to increase the arterial pressures produced by the chest compressions, thereby increasing perfusion of brain and myocardium at the expense of peripheral organs and tissues. The most widely used vasoconstrictors include epinephrine, a physiological adrenergic agonist, and vasopressin, a non-adrenergic vasoconstrictor which may afford greater survival to hospital discharge than epinephrine, especially in patients with asystole^[51,52].

Although epinephrine has been used in this manner for decades, its potentially detrimental effects, including increased physiological shunt compromising pulmonary gas exchange^[53,54], intensified myocardial ATP consumption and oxygen demand^[55], and the resultant post-resuscitation myocardial dysfunction^[56] and ventricular arrhythmias^[57,58] have raised concerns regarding its clinical application for CPR. Preclinical and clinical evidence has shown the non-adrenergic vasoconstrictor vasopressin to be at least as effective as epinephrine at augmenting arterial pressure during precordial compressions, but without epinephrine's untoward effects. In a porcine cardiac arrest model, vasopressin vs epinephrine produced greater myocardial and brain blood flows and mean arterial pressures during CPR^[59]. Thus, vasopressin was associated with higher incidence of conversion to productive sinus rhythm^[60], increased post-arrest cardiac function and decreased morbidity and mortality vs epinephrine. We have found^[61] that vasopressin (c. 0.3 U/kg) injected into the right jugular vein at 60 s CPR improved markedly the quality of CPR, increasing the mean arterial pressures from 25-30 to c. 60 mmHg within 3 min (*cf.* Figure 1). Although epinephrine produced a more abrupt increase in arterial pressure following its injection, within 2 min vasopressin increased mean arterial pressure to a similar extent; during the first 15 min ROSC, the vasopressin-treated swine

had less intense tachycardia and more moderate heart rate x arterial pressure product, a measure of myocardial energy expenditure, than their epinephrine-treated counterparts^[61].

Defibrillation and cardioversion

The defibrillation protocol presents the investigator several options for model design. One choice is the sequence of defibrillatory countershocks, *i.e.*, whether the shocks will be administered singly, or in a sequence of multiple (often three) countershocks, before checking for cardioversion. The electrical energies of the countershocks must be considered, including that of the initial countershock, and, if the initial shock fails to achieve cardioversion, whether or at what progression the intensity will be increased for subsequent countershocks. It must be determined if and for how long CPR will be administered during the interval between an unsuccessful cardioversion and the next attempt. When pre-CPR arrest exceeds the electrical phase, bouts of CPR, including a minimum of 20-25 s of chest compressions following unsuccessful countershocks, are essential to ensure effective countershocks. A similar protocol of single shocks with intervening chest compressions increased post-arrest survival vs a conventional 3-shock protocol in a porcine model of ventricular fibrillation cardiac arrest^[25].

The cardiocirculatory values that constitute ROSC, including the presence of an organized electrical rhythm and maintenance of arterial blood pressure above a predetermined target value for a minimum duration (*cf.* Table 1) must be specified. Core body temperature has a marked effect on post-arrest and neurological injury and mortality; indeed, moderate hypothermia is the only currently approved intervention consistently shown to produce significant clinical benefit^[62-64]. Pigs do not thermoregulate effectively while under anesthesia, so typically the animal must be maintained on a heating pad during the cardiac arrest-resuscitation protocol to avoid the impact of hypothermia on study endpoints. Finally, the criteria for abandoning futile resuscitation efforts must be defined.

Post-resuscitation management

Because cardiac arrest imposes ischemia on the heart itself, cardiac mechanical function may be depressed for several hours of ROSC, a manifestation of reversible myocardial injury termed cardiac "stunning"^[65]. As the period of ROSC progresses, interventions may be necessary to maintain adequate arterial pressure. Intravenous saline solutions may be infused to expand extracellular fluid volume. Vasopressor agents, *e.g.*, phenylephrine, may be administered, but it should be recognized that vasopressors may lose their efficacy over time due to desensitization of their membrane receptors^[66] and, thus, may be unsuitable for long-

term maintenance of arterial pressure. Accordingly, the vasoconstrictor infusion can be tapered and ultimately discontinued as cardiac function recovers. It may be necessary to adjust tidal volume and frequency of ventilations or administer bicarbonate to compensate for post-arrest hypercapnia and/or acidemia. Isotonic saline (0.9% NaCl) may be infused *iv* to maintain extracellular fluid volume over the course of the protocol.

Inspired oxygen concentration

The oxygen concentration of medical gases used during resuscitation is an important consideration when designing a model of cardiac arrest-resuscitation. For decades, it has been recommended that patients be ventilated with 100% oxygen during resuscitation to increase oxygen delivery to ischemic tissues^[67,68]. Recently, however, hyperoxic ventilation during resuscitation has been shown to intensify formation of reactive oxygen and nitrogen intermediates within tissues and, thus, exacerbate ischemia-reperfusion injury^[69-75]. A recent meta-analysis of clinical trial data showed hyperoxia (PaO₂ > 300 mmHg) to be associated with increased in-hospital mortality following cardiac arrest^[76]. Oxygen toxicity has been studied for years in a perioperative setting, but only recently has there been sufficient clinical evidence for the European Resuscitation Council to recommend that patients not be ventilated with 100% oxygen after cardiac arrest, but rather with room air supplemented with enough O₂ to maintain an oxyhemoglobin saturation (spO₂) of 94%-98%^[77,78]. Thus, when designing a cardiac arrest model, the oxygen concentration used during resuscitation may be adjusted depending on whether the study aims to mimic the conventional approach of ventilation with 100% oxygen, or newly recommended strategies such as titration of oxygen administration to maintain a desired spO₂.

CHALLENGES TO MODELING CARDIAC ARREST IN PIGS

Pulseless electrical activity

Pulseless electrical activity (PEA) is a "non-shockable" cardiac electrical rhythm that does not produce ventricular contraction or forward movement of blood. Approximately 60% of out-of-hospital resuscitation attempts result in the development of PEA as the presenting rhythm^[79]. Only 2%-5% of patients who present with PEA as their initial rhythm survive to hospital discharge^[80-82], well below the 15%-40% survival rate of those presenting with ventricular fibrillation^[83-85]. Even fewer patients in whom ventricular fibrillation converted to PEA following countershocks survive to hospital discharge^[79,86]. In our porcine cardiac arrest model, PEA is an ominous finding; typically, even heroic

efforts fail to convert PEA to a productive sinus rhythm. None of the 9 pigs developing PEA during resuscitative efforts survived for 4 h ROSC. This situation replicates the clinical setting of out-of-hospital cardiac arrest, where a much lower rate of survival to hospital discharge is achieved in cardiac arrest victims in which PEA is the initial rhythm vs patients with an initial electrocardiographic substrate of ventricular fibrillation^[87].

Malignant hyperthermia

A small minority of pigs harbor a genetic lesion in the skeletal muscle sarcoplasmic reticular Ca²⁺ release channels^[88,89] that predisposes them to develop malignant hyperthermia (*aka* porcine stress syndrome), often triggered by exposure to volatile anesthetics^[90]. Malignant hyperthermia has no overt clinical phenotype detectable by routine screening. As post-arrest survival and neurobehavioral recovery are negatively correlated with body temperature, an episode of malignant hyperthermia, during which core body temperature may rise above 42 °C, can have disastrous consequences, including systemic hypotension, acidemia, hypercapnia and hyperkalemia that are refractory to conventional interventions. Indeed, in our studies none of the five anesthetized pigs (4% of the total) that developed acute malignant hyperthermia survived to 4 h ROSC, despite aggressive measures including intravenous infusion of ice-cold saline and the K⁺ chelator calcium gluconate.

Limitations of porcine models

An important limitation of many porcine cardiac arrest models is that juvenile, disease-free pigs are generally used. In clinical settings, patients who experience cardiac arrest typically are elderly and suffer from chronic disorders such as hypertension, atherosclerosis, congestive heart failure, diabetes, emphysema or end-stage renal disease. The Ossabaw swine, which is predisposed to develop metabolic syndrome when consuming a high fat diet^[91,92], provides a unique, clinically relevant experimental model suitable for studying cardiac arrest and resuscitation superimposed on metabolic syndrome. Indeed, under anesthesia these swine develop severe arrhythmias, responsive to amiodarone, that may deteriorate into cardiac arrest (Johnathan D. Tune, personal communication).

Unlike most porcine preparations, human victims of out-of-hospital cardiac arrest are not anesthetized when they are stricken. Cardiac arrest is an unanticipated event, and when it occurs outside the hospital, the delays to effective treatments are variable, poorly defined and all too often lethal. Most preclinical cardiac arrest studies employ well defined protocols, such as those reviewed herein. The fundamental differences between these protocols

and the highly variable and exceedingly challenging clinical situation must be acknowledged.

CONCLUSION

Over the last few decades the collective efforts of many investigators have fostered the development of sophisticated porcine models of cardiac arrest, CPR and ROSC. The domestic pig provides an excellent large animal model of the human cardiovascular system and yields ample tissue for extensive analyses of mechanisms of injury and cytoprotection in the internal organs, such that each experiment generates a wealth of information. Although there is much to consider when constructing an experimental design, the swine model of cardiac arrest-resuscitation is easily tailored to accommodate the desired study end points. The swine model provides unparalleled translational value among current mammalian models of cardiac arrest and CPR, permitting an integrative approach to bridge the gap from bench to bedside.

ACKNOWLEDGMENTS

The authors thank Egeenee Q. Daniels, DVM, Arthur G. Williams, Jr., BS, Shirley R. Nelson, RLAT, and Besim Hoxha, MD for their expert advice and assistance in helping develop and refine their porcine cardiac arrest-resuscitation preparation.

REFERENCES

- 1 **Kouwenhoven WB**, Milnor WR, Knickerbocker GG, Chesnut WR. Closed chest defibrillation of the heart. *Surgery* 1957; **42**: 550-561 [PMID: 13467613]
- 2 **Dezfulian C**, Shiva S, Alekseyenko A, Pendyal A, Beiser DG, Munasinghe JP, Anderson SA, Chesley CF, Vanden Hoek TL, Gladwin MT. Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. *Circulation* 2009; **120**: 897-905 [PMID: 19704094 DOI: 10.1161/CIRCULATIONAHA.109.853267]
- 3 **Young GB**. Clinical practice. Neurologic prognosis after cardiac arrest. *N Engl J Med* 2009; **361**: 605-611 [PMID: 19657124 DOI: 10.1056/NEJMcip0903466]
- 4 **Heron M**. Deaths: leading causes for 2009. *Natl Vital Stat Rep* 2012; **61**: 1-94 [PMID: 24964584]
- 5 **Nolan JP**, Lyon RM, Sasson C, Rossetti AO, Lansky AJ, Fox KA, Meier P. Advances in the hospital management of patients following an out of hospital cardiac arrest. *Heart* 2012; **98**: 1201-1206 [PMID: 22649095 DOI: 10.1136/heartjnl-2011-301293]
- 6 **Adrie C**, Laurent I, Monchi M, Cariou A, Dhainaut JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care* 2004; **10**: 208-212 [PMID: 15166838 DOI: 10.1097/01.ccx.0000126090.06275.fe]
- 7 **Stubb D**, Bernard S, Duffy SJ, Kaye DM. Post cardiac arrest syndrome: a review of therapeutic strategies. *Circulation* 2011; **123**: 1428-1435 [PMID: 21464058 DOI: 10.1161/CIRCULATIONAHA.110.988725]
- 8 **Corry JJ**. Use of hypothermia in the intensive care unit. *World J Crit Care Med* 2012; **1**: 106-122 [PMID: 24701408 DOI: 10.5492/wjccm.v1.i4.106]
- 9 **White BC**, Sullivan JM, DeGracia DJ, O'Neil BJ, Neumar RW, Grossman LI, Rafols JA, Krause GS. Brain ischemia and reperfusion: molecular mechanisms of neuronal injury. *J Neurol Sci* 2000; **179**: 1-33 [PMID: 11054482 DOI: 10.1016/S0022-510X(00)00386-5]
- 10 **Nguyen AQ**, Cherry BH, Scott GF, Ryou MG, Mallet RT. Erythropoietin: powerful protection of ischemic and post-ischemic brain. *Exp Biol Med* (Maywood) 2014; **239**: 1461-1475 [PMID: 24595981 DOI: 10.1177/1535370214523703]
- 11 **Xanthos T**, Lelovas P, Vlachos I, Tsiros-Karapanos N, Kouskouni E, Perrea D, Dontas I. Cardiopulmonary arrest and resuscitation in Landrace/White swine: a research model. *Lab Anim* 2007; **41**: 353-362 [PMID: 17640463 DOI: 10.1258/002367707781282820]
- 12 **Walters EM**, Agca Y, Ganjam V, Evans T. Animal models got you puzzled?: think pig. *Ann N Y Acad Sci* 2011; **1245**: 63-64 [PMID: 22211982 DOI: 10.1111/j.1749-6632.2011.06345.x]
- 13 **Brecher MM**, Dworken AM. The Merck Manual. *Med Herit* 1986; **2**: 229-231 [PMID: 11611983]
- 14 **American Association for Laboratory Animal Science**. Normative biological data for common laboratory animal species. In: ALAT training manual. Memphis, TN: American Association for Laboratory Animal Science, 2009: 242-243
- 15 **Bildfell RJ**. Collection and submission of laboratory samples. The Merck veterinary manual. 10th ed. Whitehouse Station, NJ: Merck & Co., Inc., 2010: 1463-1469
- 16 **Bircher N**, Safar P. Cerebral preservation during cardiopulmonary resuscitation. *Crit Care Med* 1985; **13**: 185-190 [PMID: 3971729 DOI: 10.1097/00003246-198503000-00009]
- 17 **Benson DM**, O'Neil B, Kakish E, Erpelding J, Alousi S, Mason R, Piper D, Rafols J. Open-chest CPR improves survival and neurologic outcome following cardiac arrest. *Resuscitation* 2005; **64**: 209-217 [PMID: 15680532 DOI: 10.1016/j.resuscitation.2003.03.001]
- 18 **Newman B**, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. *Anesthesiology* 1986; **64**: 307-310 [PMID: 3082250 DOI: 10.1097/0000542-198603000-00001]
- 19 **Lessard MR**, Trépanier CA. Renal function and hemodynamics during prolonged isoflurane-induced hypotension in humans. *Anesthesiology* 1991; **74**: 860-865 [PMID: 2021202 DOI: 10.1097/0000542-199105000-00010]
- 20 **Matta BF**, Lam AM, Mayberg TS, Eng CC, Strebel S. Cerebrovascular response to carbon dioxide during sodium nitroprusside- and isoflurane-induced hypotension. *Br J Anaesth* 1995; **74**: 296-300 [PMID: 7718375 DOI: 10.1093/bja/74.3.296]
- 21 **Hoffman WE**, Edelman G, Ripper R, Koenig HM. Sodium nitroprusside compared with isoflurane-induced hypotension: the effects on brain oxygenation and arteriovenous shunting. *Anesth Analg* 2001; **93**: 166-170 [PMID: 11429359 DOI: 10.1097/00000539-200107000-00033]
- 22 **Kato R**, Foëx P. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. *Can J Anaesth* 2002; **49**: 777-791 [PMID: 12374705 DOI: 10.1007/BF03017409]
- 23 **Landoni G**, Fochi O, Torri G. Cardiac protection by volatile anaesthetics: a review. *Curr Vasc Pharmacol* 2008; **6**: 108-111 [PMID: 18393912 DOI: 10.2174/157016108783955284]
- 24 **Geddes LA**, Roeder RA, Rundell AE, Otlewski MP, Kemeny AE, Lottes AE. The natural biochemical changes during ventricular fibrillation with cardiopulmonary resuscitation and the onset of postdefibrillation pulseless electrical activity. *Am J Emerg Med* 2006; **24**: 577-581 [PMID: 16938597 DOI: 10.1016/j.ajem.2006.01.030]
- 25 **Tang W**, Snyder D, Wang J, Huang L, Chang YT, Sun S, Weil MH. One-shock versus three-shock defibrillation protocol significantly improves outcome in a porcine model of prolonged ventricular fibrillation cardiac arrest. *Circulation* 2006; **113**: 2683-2689 [PMID: 16754801 DOI: 10.1161/CIRCULATIONAHA.105.592121]
- 26 **Ewy GA**, Zuercher M, Hilwig RW, Sanders AB, Berg RA, Otto CW, Hayes MM, Kern KB. Improved neurological outcome with continuous chest compressions compared with 30: 2 compressions-

- to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest. *Circulation* 2007; **116**: 2525-2530 [PMID: 17998457 DOI: 10.1161/CIRCULATIONAHA.107.711820]
- 27 **Wu CJ**, Li CS, Zhang Y, Yang J, Yin Q, Hang CC. Differences of postresuscitation myocardial dysfunction in ventricular fibrillation versus asphyxiation. *Am J Emerg Med* 2013; **31**: 1690-1696 [PMID: 24041641 DOI: 10.1016/j.ajem.2013.08.017]
 - 28 **Niemann JT**, Rosborough JP, Youngquist ST, Shah AP. Transthoracic defibrillation potential gradients in a closed chest porcine model of prolonged spontaneous and electrically induced ventricular fibrillation. *Resuscitation* 2010; **81**: 477-480 [PMID: 20122785 DOI: 10.1016/j.resuscitation.2009.12.027]
 - 29 **Wang J**, Weil MH, Tang W, Chang YT, Huang L. A comparison of electrically induced cardiac arrest with cardiac arrest produced by coronary occlusion. *Resuscitation* 2007; **72**: 477-483 [PMID: 17134815 DOI: 10.1016/j.resuscitation.2006.06.041]
 - 30 **Lancaster LD**, Kern KB, Morrison DA, Olajos M, Goldman S. Changes in right ventricular relaxation during acute anterior myocardial infarction in pigs. *Cardiovasc Res* 1989; **23**: 46-52 [PMID: 2776150 DOI: 10.1093/cvr/23.1.46]
 - 31 **Indik JH**, Allen D, Shanmugasundaram M, Zuercher M, Hilwig RW, Berg RA, Kern KB. Predictors of resuscitation in a swine model of ischemic and nonischemic ventricular fibrillation cardiac arrest: superiority of amplitude spectral area and slope to predict a return of spontaneous circulation when resuscitation efforts are prolonged. *Crit Care Med* 2010; **38**: 2352-2357 [PMID: 20890198 DOI: 10.1097/CCM.0b013e3181fa01ee]
 - 32 **Qin H**, Walcott GP, Killingsworth CR, Rollins DL, Smith WM, Ideker RE. Impact of myocardial ischemia and reperfusion on ventricular defibrillation patterns, energy requirements, and detection of recovery. *Circulation* 2002; **105**: 2537-2542 [PMID: 12034662 DOI: 10.1161/01.CIR.0000016702.86180.F6]
 - 33 **Walcott GP**, Killingsworth CR, Smith WM, Ideker RE. Biphasic waveform external defibrillation thresholds for spontaneous ventricular fibrillation secondary to acute ischemia. *J Am Coll Cardiol* 2002; **39**: 359-365 [PMID: 11788232 DOI: 10.1016/S0735-1097(01)01723-5]
 - 34 **Voelckel WG**, Lurie KG, McKnite S, Zielinski T, Lindstrom P, Peterson C, Krismer AC, Lindner KH, Wenzel V. Comparison of epinephrine and vasopressin in a pediatric porcine model of asphyxial cardiac arrest. *Crit Care Med* 2000; **28**: 3777-3783 [PMID: 11153614 DOI: 10.1097/00003246-200012000-00001]
 - 35 **Varvarousi G**, Goulas S, Agogiannis G, Valsamakis N, Iliopoulos D, Perrea D, Stefanadis C, Papadimitriou L, Xanthos T. Epinephrine, vasopressin, and nitroglycerin improve neurologic outcome in porcine asphyxial cardiac arrest. *Am J Emerg Med* 2012; **30**: 1549-1554 [PMID: 22386348 DOI: 10.1016/j.ajem.2012.01.008]
 - 36 **Sutton RM**, Friess SH, Bhalala U, Maltese MR, Naim MY, Bratinov G, Niles D, Nadkarni VM, Becker LB, Berg RA. Hemodynamic directed CPR improves short-term survival from asphyxia-associated cardiac arrest. *Resuscitation* 2013; **84**: 696-701 [PMID: 23142199 DOI: 10.1016/j.resuscitation.2012.10.023]
 - 37 **López-Herce J**, Fernández B, Urbano J, Mencía S, Solana MJ, Rodríguez-Núñez A, Bellón JM, Carrillo A. Hemodynamic, respiratory, and perfusion parameters during asphyxia, resuscitation, and post-resuscitation in a pediatric model of cardiac arrest. *Intensive Care Med* 2011; **37**: 147-155 [PMID: 20838762 DOI: 10.1007/s00134-010-2006-2]
 - 38 **Mayr VD**, Raedler C, Wenzel V, Lindner KH, Strohmenger HU. A comparison of epinephrine and vasopressin in a porcine model of cardiac arrest after rapid intravenous injection of bupivacaine. *Anesth Analg* 2004; **98**: 1426-1431, table of contents [PMID: 15105225 DOI: 10.1213/01.ANE.0000108488.05900.A8]
 - 39 **Gilmore CM**, Rea TD, Becker LJ, Eisenberg MS. Three-phase model of cardiac arrest: time-dependent benefit of bystander cardiopulmonary resuscitation. *Am J Cardiol* 2006; **98**: 497-499 [PMID: 16893704 DOI: 10.1016/j.amjcard.2006.02.055]
 - 40 **Sharma AB**, Knott EM, Bi J, Martinez RR, Sun J, Mallet RT. Pyruvate improves cardiac electromechanical and metabolic recovery from cardiopulmonary arrest and resuscitation. *Resuscitation* 2005; **66**: 71-81 [PMID: 15993732 DOI: 10.1016/j.resuscitation.2004.12.016]
 - 41 **Abella BS**, Sandbo N, Vassilatos P, Alvarado JP, O'Hearn N, Wigder HN, Hoffman P, Tynus K, Vanden Hoek TL, Becker LB. Chest compression rates during cardiopulmonary resuscitation are suboptimal: a prospective study during in-hospital cardiac arrest. *Circulation* 2005; **111**: 428-434 [PMID: 15687130 DOI: 10.1161/01.CIR.0000153811.84257.59]
 - 42 **Ristagno G**, Tang W, Chang YT, Jorgenson DB, Russell JK, Huang L, Wang T, Sun S, Weil MH. The quality of chest compressions during cardiopulmonary resuscitation overrides importance of timing of defibrillation. *Chest* 2007; **132**: 70-75 [PMID: 17550931 DOI: 10.1378/chest.06-3065]
 - 43 **Idris AH**, Guffey D, Aufderheide TP, Brown S, Morrison LJ, Nichols P, Powell J, Daya M, Bigham BL, Atkins DL, Berg R, Davis D, Stiell I, Sopko G, Nichol G. Relationship between chest compression rates and outcomes from cardiac arrest. *Circulation* 2012; **125**: 3004-3012 [PMID: 22623717 DOI: 10.1161/CIRCULATIONAHA.111.059535]
 - 44 **Wallace SK**, Abella BS, Becker LB. Quantifying the effect of cardiopulmonary resuscitation quality on cardiac arrest outcome: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 148-156 [PMID: 23481533 DOI: 10.1161/CIRCOUTCOMES.111.000041]
 - 45 **Meaney PA**, Bobrow BJ, Mancini ME, Christenson J, de Caen AR, Bhanji F, Abella BS, Kleinman ME, Edelson DP, Berg RA, Aufderheide TP, Menon V, Leary M. Cardiopulmonary resuscitation quality: improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. *Circulation* 2013; **128**: 417-435 [PMID: 23801105 DOI: 10.1161/CIR.0b013e31829d8654]
 - 46 **Bohm K**, Rosenqvist M, Herlitz J, Hollenberg J, Svensson L. Survival is similar after standard treatment and chest compression only in out-of-hospital bystander cardiopulmonary resuscitation. *Circulation* 2007; **116**: 2908-2912 [PMID: 18071077 DOI: 10.1161/CIRCULATIONAHA.107.710194]
 - 47 **Iwami T**, Kawamura T, Hiraide A, Berg RA, Hayashi Y, Nishiuchi T, Kajino K, Yonemoto N, Yukioka H, Sugimoto H, Kakuchi H, Sase K, Yokoyama H, Nonogi H. Effectiveness of bystander-initiated cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation* 2007; **116**: 2900-2907 [PMID: 18071072 DOI: 10.1161/CIRCULATIONAHA.107.723411]
 - 48 **Berger S**. Gasping, survival, and the science of resuscitation. *Circulation* 2008; **118**: 2495-2497 [PMID: 19064691 DOI: 10.1161/CIRCULATIONAHA.108.823203]
 - 49 **Nagao K**. Chest compression-only cardiocerebral resuscitation. *Curr Opin Crit Care* 2009; **15**: 189-197 [PMID: 19451816 DOI: 10.1097/MCC.0b013e3283295f2c]
 - 50 **Rea TD**, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, Bloomingdale M, Subido C, Romines S, Eisenberg MS. CPR with chest compression alone or with rescue breathing. *N Engl J Med* 2010; **363**: 423-433 [PMID: 20818863 DOI: 10.1056/NEJMoa0908993]
 - 51 **Wenzel V**, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; **350**: 105-113 [PMID: 14711909 DOI: 10.1056/NEJMoa025431]
 - 52 **Mentzelopoulos SD**, Zakyntinos SG, Siempos I, Malachias S, Ulmer H, Wenzel V. Vasopressin for cardiac arrest: meta-analysis of randomized controlled trials. *Resuscitation* 2012; **83**: 32-39 [PMID: 21787738 DOI: 10.1016/j.resuscitation.2011.07.015]
 - 53 **Tang W**, Weil MH, Gazmuri RJ, Sun S, Duggal C, Bisera J. Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation. *Circulation* 1991; **84**: 2101-2107 [PMID: 1657450 DOI: 10.1161/01.CIR.84.5.2101]
 - 54 **Thrush DN**, Downs JB, Smith RA. Is epinephrine contraindicated during cardiopulmonary resuscitation? *Circulation* 1997; **96**: 2709-2714 [PMID: 9355913 DOI: 10.1161/01.CIR.96.8.2709]
 - 55 **Ditchey RV**, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. *Circulation* 1988; **78**: 382-389

- [PMID: 3396175 DOI: 10.1161/01.CIR.78.2.382]
- 56 **Tang W**, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the severity of postresuscitation myocardial dysfunction. *Circulation* 1995; **92**: 3089-3093 [PMID: 7586280 DOI: 10.1161/01.CIR.92.10.3089]
 - 57 **Niemann JT**, Haynes KS, Garner D, Rennie CJ, Jagels G, Stormo O. Postcountershock pulseless rhythms: response to CPR, artificial cardiac pacing, and adrenergic agonists. *Ann Emerg Med* 1986; **15**: 112-120 [PMID: 3511782 DOI: 10.1016/S0196-0644(86)80003-8]
 - 58 **Tovar OH**, Jones JL. Epinephrine facilitates cardiac fibrillation by shortening action potential refractoriness. *J Mol Cell Cardiol* 1997; **29**: 1447-1455 [PMID: 9201629 DOI: 10.1006/jmcc.1997.0387]
 - 59 **Lindner KH**, Brinkmann A, Pfenninger EG, Lurie KG, Goertz A, Lindner IM. Effect of vasopressin on hemodynamic variables, organ blood flow, and acid-base status in a pig model of cardiopulmonary resuscitation. *Anesth Analg* 1993; **77**: 427-435 [PMID: 8368541 DOI: 10.1213/00000539-199309000-00003]
 - 60 **Wenzel V**, Lindner KH, Krismer AC, Miller EA, Voelckel WG, Lingnau W. Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs. *Circulation* 1999; **99**: 1379-1384 [PMID: 10077524 DOI: 10.1161/01.CIR.99.10.1379]
 - 61 **Cherry BH**, Nguyen AQ, Williams AG Jr., Scott GF, Hollrah RA, Ryou MG, Hoxha B, Olivencia-Yurvati AH, Mallet RT. Vasopressin instead of epinephrine enhances efficacy of CPR without causing tachycardia. *FASEB J* 2014; **28**: 1150-1150.5
 - 62 **Dumas F**, White L, Stubbs BA, Cariou A, Rea TD. Long-term prognosis following resuscitation from out of hospital cardiac arrest: role of percutaneous coronary intervention and therapeutic hypothermia. *J Am Coll Cardiol* 2012; **60**: 21-27 [PMID: 22742398 DOI: 10.1016/j.jacc.2012.03.036]
 - 63 **Hörburger D**, Testori C, Sterz F, Herkner H, Krizanac D, Uray T, Schober A, Stöckl M, Stratil P, Weiser C, Wallmüller C, Holzer M. Mild therapeutic hypothermia improves outcomes compared with normothermia in cardiac-arrest patients—a retrospective chart review. *Crit Care Med* 2012; **40**: 2315-2319 [PMID: 22622403 DOI: 10.1097/CCM.0b013e31825333cf]
 - 64 **Wang CJ**, Yang SH, Lee CH, Lin RL, Peng MJ, Wu CL. Therapeutic hypothermia application vs standard support care in post resuscitated out-of-hospital cardiac arrest patients. *Am J Emerg Med* 2013; **31**: 319-325 [PMID: 23158613 DOI: 10.1016/j.ajem.2012.08.024]
 - 65 **Laurent I**, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, Dhainaut JF. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002; **40**: 2110-2116 [PMID: 12505221 DOI: 10.1016/S0735-1097(02)02594-9]
 - 66 **Chalothorn D**, McCune DF, Edelmann SE, Garcia-Cazarin ML, Tsujimoto G, Piascik MT. Differences in the cellular localization and agonist-mediated internalization properties of the alpha(1)-adrenoceptor subtypes. *Mol Pharmacol* 2002; **61**: 1008-1016 [PMID: 11961118 DOI: 10.1124/mol.61.5.1008]
 - 67 **Smith J**, Penninckx JJ, Kampschulte S, Safar P. Need for oxygen enrichment in myocardial infarction, shock and following cardiac arrest. *Acta Anaesthesiol Scand Suppl* 1968; **29**: 127-145 [PMID: 4877219 DOI: 10.1111/j.1399-6576.1968.tb00730.x]
 - 68 **O'Driscoll BR**, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; **63** Suppl 6: vi1-v68 [PMID: 18838559 DOI: 10.1136/thx.2008.102947]
 - 69 **Mantell LL**, Lee PJ. Signal transduction pathways in hyperoxia-induced lung cell death. *Mol Genet Metab* 2000; **71**: 359-370 [PMID: 11001828 DOI: 10.1006/mgme.2000.3046]
 - 70 **Richards EM**, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. *Stroke* 2007; **38**: 1578-1584 [PMID: 17413048 DOI: 10.1161/STROKEAHA.106.473967]
 - 71 **Richards EM**, Rosenthal RE, Kristian T, Fiskum G. Posts ischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity. *Free Radic Biol Med* 2006; **40**: 1960-1970 [PMID: 16716897 DOI: 10.1016/j.freeradbiomed.2006.01.022]
 - 72 **Koch JD**, Miles DK, Gilley JA, Yang CP, Kernie SG. Brief exposure to hyperoxia depletes the glial progenitor pool and impairs functional recovery after hypoxic-ischemic brain injury. *J Cereb Blood Flow Metab* 2008; **28**: 1294-1306 [PMID: 18334993 DOI: 10.1038/jcbfm.2008.15]
 - 73 **Kilgannon JH**, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, Shapiro NI, Trzeciak S. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. *Circulation* 2011; **123**: 2717-2722 [PMID: 21606393 DOI: 10.1161/CIRCULATIONAHA.110.001016]
 - 74 **Pilcher J**, Weatherall M, Shirlcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials. *Resuscitation* 2012; **83**: 417-422 [PMID: 22226734 DOI: 10.1016/j.resuscitation.2011.12.021]
 - 75 **Solberg R**, Longini M, Proietti F, Vezzosi P, Saugstad OD, Buonocore G. Resuscitation with supplementary oxygen induces oxidative injury in the cerebral cortex. *Free Radic Biol Med* 2012; **53**: 1061-1067 [PMID: 22842050 DOI: 10.1016/j.freeradbiomed.2012.07.022]
 - 76 **Wang CH**, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, Chen NC, Chen WJ. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. *Resuscitation* 2014; **85**: 1142-1148 [PMID: 24892265 DOI: 10.1016/j.resuscitation.2014.05.021]
 - 77 **Balan IS**, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE. Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest. *Stroke* 2006; **37**: 3008-3013 [PMID: 17068310 DOI: 10.1161/01.STR.0000248455.73785.b1]
 - 78 **Deakin CD**, Nolan JP, Soar J, Sunde K, Koster RW, Smith GB, Perkins GD. European Resuscitation Council Guidelines for Resuscitation 2010 Section 4. Adult advanced life support. *Resuscitation* 2010; **81**: 1305-1352 [PMID: 20956049 DOI: 10.1016/j.resuscitation.2010.08.017]
 - 79 **Niemann JT**, Stratton SJ, Cruz B, Lewis RJ. Outcome of out-of-hospital postcountershock asystole and pulseless electrical activity versus primary asystole and pulseless electrical activity. *Crit Care Med* 2001; **29**: 2366-2370 [PMID: 11801841 DOI: 10.1097/00003246-200112000-00020]
 - 80 **Rea TD**, Eisenberg MS, Sinibaldi G, White RD. Incidence of EMS-treated out-of-hospital cardiac arrest in the United States. *Resuscitation* 2004; **63**: 17-24 [PMID: 15451582 DOI: 10.1016/j.resuscitation.2004.03.025]
 - 81 **Atwood C**, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005; **67**: 75-80 [PMID: 16199289 DOI: 10.1016/j.resuscitation.2005.03.021]
 - 82 **Kajino K**, Iwami T, Daya M, Nishiuchi T, Hayashi Y, Ikeuchi H, Tanaka H, Shimazu T, Sugimoto H. Subsequent ventricular fibrillation and survival in out-of-hospital cardiac arrests presenting with PEA or asystole. *Resuscitation* 2008; **79**: 34-40 [PMID: 18678438 DOI: 10.1016/j.resuscitation.2008.05.017]
 - 83 **Rea TD**, Helbock M, Perry S, Garcia M, Cloyd D, Becker L, Eisenberg M. Increasing use of cardiopulmonary resuscitation during out-of-hospital ventricular fibrillation arrest: survival implications of guideline changes. *Circulation* 2006; **114**: 2760-2765 [PMID: 17159062 DOI: 10.1161/CIRCULATIONAHA.106.654715]
 - 84 **Nichol G**, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; **300**: 1423-1431 [PMID: 18812533 DOI: 10.1001/jama.300.12.1423]
 - 85 **Garza AG**, Gratton MC, Salomone JA, Lindholm D, McElroy J, Archer R. Improved patient survival using a modified resuscitation protocol for out-of-hospital cardiac arrest. *Circulation* 2009; **119**: 2597-2605 [PMID: 19414637 DOI: 10.1161/CIRCULATIONAHA.108.815621]
 - 86 **Warner LL**, Hoffman JR, Baraff LJ. Prognostic significance of field response in out-of-hospital ventricular fibrillation. *Chest* 1985; **87**: 22-28 [PMID: 3965262 DOI: 10.1378/chest.87.1.22]

- 87 **Eisenberg MS**, Mengert TJ. Cardiac resuscitation. *N Engl J Med* 2001; **344**: 1304-1313 [PMID: 11320390 DOI: 10.1056/NEJM200104263441707]
- 88 **Fujii J**, Otsu K, Zorzato F, de Leon S, Khanna VK, Weiler JE, O'Brien PJ, MacLennan DH. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science* 1991; **253**: 448-451 [PMID: 1862346 DOI: 10.1126/science.1862346]
- 89 **Mickelson JR**, Louis CF. Malignant hyperthermia: excitation-contraction coupling, Ca^{2+} release channel, and cell Ca^{2+} regulation defects. *Physiol Rev* 1996; **76**: 537-592 [PMID: 8618963]
- 90 **Liou YM**, Jiang MJ, Wu MC. Altered expression of cardiac myosin isoforms associated with the malignant hyperthermia genotype in swine. *Anesthesiology* 2000; **93**: 1312-1319 [PMID: 11046221 DOI: 10.1097/00000542-200011000-00026]
- 91 **Borbouse L**, Dick GM, Payne GA, Berwick ZC, Neeb ZP, Alloosh M, Bratz IN, Sturek M, Tune JD. Metabolic syndrome reduces the contribution of K^{+} channels to ischemic coronary vasodilation. *Am J Physiol Heart Circ Physiol* 2010; **298**: H1182-H1189 [PMID: 20118408 DOI: 10.1152/ajpheart.00888.2009]
- 92 **Trask AJ**, Katz PS, Kelly AP, Galantowicz ML, Cismowski MJ, West TA, Neeb ZP, Berwick ZC, Goodwill AG, Alloosh M, Tune JD, Sturek M, Lucchesi PA. Dynamic micro- and macrovascular remodeling in coronary circulation of obese Ossabaw pigs with metabolic syndrome. *J Appl Physiol* (1985) 2012; **113**: 1128-1140 [PMID: 22837170 DOI: 10.1152/japplphysiol.00604.2012]
- 93 **Lurie KG**, Zielinski T, McKnite S, Aufderheide T, Voelckel W. Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation. *Circulation* 2002; **105**: 124-129 [PMID: 11772887 DOI: 10.1161/hc0102.101391]
- 94 **Li Y**, Ristagno G, Bisera J, Tang W, Deng Q, Weil MH. Electrocardiogram waveforms for monitoring effectiveness of chest compression during cardiopulmonary resuscitation. *Crit Care Med* 2008; **36**: 211-215 [PMID: 18090357 DOI: 10.1097/01.CCM.0000295594.93345.A2]
- 95 **Indik JH**, Shanmugasundaram M, Allen D, Valles A, Kern KB, Hilwig RW, Zuercher M, Berg RA. Predictors of resuscitation outcome in a swine model of VF cardiac arrest: A comparison of VF duration, presence of acute myocardial infarction and VF waveform. *Resuscitation* 2009; **80**: 1420-1423 [PMID: 19804932 DOI: 10.1016/j.resuscitation.2009.08.023]
- 96 **Hang CC**, Li CS, Wu CJ, Yang J. Acute kidney injury after cardiac arrest of ventricular fibrillation and asphyxiation swine model. *Am J Emerg Med* 2014; **32**: 208-215 [PMID: 24361141 DOI: 10.1016/j.ajem.2013.10.043]

P- Reviewer: Lin J, Yao YM **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Wu HL



Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us

Yu-Zhi Zhang, Suveer Singh

Yu-Zhi Zhang, Suveer Singh, Departments of Intensive Care and Respiratory Medicine, Chelsea and Westminster Hospital, London SW10 9NH, United Kingdom

Author contributions: Singh S conceived and designed the article; Zhang YZ wrote the first draft; Zhang YZ and Singh S extracted and reviewed the studies in the Systematic analysis; Zhang YZ and Singh S revised the manuscript; Singh S rewrote the final revised version.

Conflict-of-interest: The authors declare that they have no competing interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Suveer Singh, BSc, MBBS, PhD, EDIC, DICM, FFICM, FRCP, Departments of Intensive Care and Respiratory Medicine, Chelsea and Westminster Hospital, 369 Fulham Rd, London SW10 9NH,

United Kingdom. suveer.singh@imperial.ac.uk

Telephone: +44-208-7468472

Fax: +44-208-7468040

Received: October 7, 2014

Peer-review started: October 8, 2014

First decision: November 19, 2014

Revised: November 21, 2014

Accepted: December 16, 2014

Article in press: December 17, 2014

Published online: February 4, 2015

Abstract

Antibiotic usage and increasing antimicrobial resistance (AMR) mount significant challenges to patient safety and management of the critically ill on intensive care units (ICU). Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment whilst minimising antibiotic resistance. Different models of ASP

in intensive care setting, include "standard" control of antibiotic prescribing such as "de-escalation strategies" through to interventional approaches utilising biomarker-guided antibiotic prescribing. A systematic review of outcomes related studies for ASPs in an ICU setting was conducted. Forty three studies were identified from MEDLINE between 1996 and 2014. Of 34 non-protocolised studies, [1 randomised control trial (RCT), 22 observational and 11 case series], 29 (85%) were positive with respect to one or more outcome: These were the key outcome of reduced antibiotic use, or ICU length of stay, antibiotic resistance, or prescribing cost burden. Limitations of non-standard antibiotic initiation triggers, patient and antibiotic selection bias or baseline demographic variance were identified. All 9 protocolised studies were RCTs, of which 8 were procalcitonin (PCT) guided antibiotic stop/start interventions. Five studies addressed antibiotic escalation, 3 de-escalation and 1 addressed both. Six studies reported positive outcomes for reduced antibiotic use, ICU length of stay or antibiotic resistance. PCT based ASPs are effective as antibiotic-stop (de-escalation) triggers, but not as an escalation trigger alone. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection. No study has demonstrated survival benefit of ASP. Ongoing challenges to infectious disease management, reported by the World Health Organisation global report 2014, are high AMR to newer antibiotics, and regional knowledge gaps in AMR surveillance. Improved AMR surveillance data, identifying core aspects of successful ASPs that are transferable, and further well-conducted trials will be necessary if ASPs are to be an effective platform for delivering desired patient outcomes and safety through best antibiotic policy.

Key words: Antibiotic stewardship programme; Intensive care; Antimicrobial resistance; Antibacterial resistance; Antibiotic resistance

© The Author(s) 2015. Published by Baishideng Publishing

Group Inc. All rights reserved.

Core tip: Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment and minimise antimicrobial resistance (AMR). Multistrategic approaches must address challenges to future management of infectious disease. Models of ASP in intensive care unit, include "standard" control of antibiotic prescribing (*e.g.*, "de-escalation strategies") through to interventional approaches utilising biomarker-guided decisions. Protocolised ASPs using procalcitonin guided antibiotic-stop but not antibiotic-start alone decisions demonstrate reduced antibiotic and AMR rates, but not survival benefit. Immediate research needs include better AMR surveillance, early microbial diagnostic tests, and core transferable elements of ASPs.

Zhang YZ, Singh S. Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us? *World J Crit Care Med* 2015; 4(1): 13-28 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/13.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.13>

BURDEN OF INFECTION IN THE CRITICALLY ILL - MAJOR CHALLENGES TO PATIENT MANAGEMENT

The intensive care unit (ICU) is often regarded as an epicentre of infections, with sepsis being the second non-cardiac cause of mortality^[1]. In two major cross-sectional studies of sepsis in the intensive care setting, Sepsis in European Intensive care units (EPIC II)^[2] and SOAP^[3], 50% and 38% of all patients respectively had infections.

Mortality from Sepsis in the critically ill can approach 50%, with time to initiation of antibiotic treatment as the single strongest predictor of outcome. Each hour's delay increases mortality by 7.6%, over the first 6 h^[4]. ICUs account for 5%-15% of total hospital beds but 10%-25% of total healthcare costs^[5]. Sepsis increases patient-related costs six-fold^[6]. In the United States, antibiotic-resistant infections are associated with 23000 deaths and 2 million illnesses per year, with estimated excess direct healthcare costs of \$20 billion and \$35 billion in lost productivity^[7]. Resistant organisms can increase patient-related prescribing costs by \$8000 to \$30000^[1]. Such empiric practice, deemed necessary at the point of care, due to uncertainty of causative organisms, is often ineffective and results in higher costs.

ANTIBIOTIC RESISTANCE IN ICU, ITS CONTRIBUTORS AND IMPACT

Antimicrobial resistance (AMR) is an increasing

global healthcare phenomenon, with apocalyptic predictions of a post-antibiotic era where common infections and minor injuries may not be treatable by conventional antibiotics^[8]. A WHO global report describes the majority of world regions with over 50% resistance of *Escherichia coli* (*E. Coli*) and *Klebsiella Pneumoniae* to 3rd generation cephalosporins and fluoroquinolones. The increasing prevalence of carbapenem-resistant organisms, and other multi-resistant strains such as Methicillin resistant *Staphylococcus aureus* (MRSA) as well as extended-spectrum beta-lactamase (ESBL) producers justifies these concerns. Specifically, AMR has a number of proposed causes. Data from United States National Nosocomial Infection Surveillance programme (NNIS) demonstrated 20%-30% increase in resistant isolates of *Pseudomonas*, *Staphylococcus aureus* and *Enterococcus* across a 5-year period^[9]. In particular, fluoroquinolone-resistant *Pseudomonas* showed more than 50% increase during the period.

Intensive care units represent the heaviest antibiotic burden within hospitals. They are described albeit provocatively, as a factory creating, disseminating and amplifying antibiotic resistance^[1]. In a European multi-centre cross-sectional prevalence study of academic ICUs, there were 14% of *Klebsiella* ESBL-producers, and nearly 25% of *Pseudomonas aeruginosa* isolates were carbapenem-resistant^[10].

ICUs in emerging economies report notably higher prevalence of ESBL-producers^[11-13] and carbapenem-resistant organisms^[11-14]. Of note, the majority of multi-resistant *Acinetobacter* (MRA) isolates in these studies also demonstrates reduced susceptibility towards carbapenems^[11-13].

The dynamics of antibiotic resistance are multifarious. Firstly, antibiotic usage in the animal and plant industry, to improve growth and productivity, is a major contributor to AMR^[15]. The increasing prevalence of ESBL producers in animal products has been suggested. Furthermore, a link between antibiotic resistance in human clinical microbiological isolates and those from poultry has been raised^[16]. On the contrary, other studies rule out such associations between chicken meat and colonisation of ESBL-producing *E. coli* in humans^[17].

Within the ICU setting itself, causes of AMR may conveniently be categorised by procedure-related, management-related, and antibiotic-related factors. Procedure-related factors include central venous catheters^[18,19] and endotracheal intubation for mechanical ventilation^[20]. Management-related factors include poor adherence to infection control policy^[20], lack of microbiological surveillance with delayed/failed recognition of resistant isolates^[21], patient overcrowding^[22,23], understaffing and implicit spread of AMR through human vectors^[24,25], prolonged ICU length of stay^[20,26], and pre-infection with resistant organisms at the time of ICU admis-

sion^[26]. Antibiotic-related factors are related to the appropriateness and duration of treatment. Non-controlled usage^[27] is well documented. Ceftriaxone for example, was shown to cause a rise in rates of vancomycin resistant *Enterococci* (VRE) rates^[28]. The use of broad-spectrum antibiotics, often as the first step in therapy for patients with suspected infections, has accumulated considerable evidence regarding its association with the development of antibiotic resistance^[20,26,29-32]. Similarly, the ease of access to certain antibiotic classes, either through their availability over-the-counter in certain countries (*i.e.*, penicillins, fluoroquinolones) or through unfounded clinician concerns of missing unlikely bacterial infection, leads to documented AMR, although causation proves difficult at an individual patient level. As such, the evidence behind the duration of treatment and AMR is comparatively lacking. In the Pneuma trial, patients with ventilator-associated pneumonia (VAP), who had prolonged antibiotic treatment (15 d vs 8 d) developed higher rates of multi-resistant *Pseudomonas* isolates^[33]. Clearly, one must be circumspect about distinguishing natural selection of antibiotic resistant bacteria through necessary antibiotic usage and judgements of inappropriate antibiotic usage as causation of AMR.

Although only shown in hospital wards rather than ICU, failure to de-escalate or discontinue therapy^[34,35] is also a likely contributory factor to antibiotic resistance in ICU.

The exact impact of multidrug resistance (MDR) microbial organisms is difficult to quantify, depend as it does on, the causative microbe and its pathogenicity, patient populations, severity of illness and the appropriateness of therapy^[36]. The association of increased ICU mortality and hospital length of stay (LOS) with MRSA, VRE, *Acinetobacter*, *Pseudomonas* and *Klebsiella* are well documented^[37]. These mirror poor outcomes associated with such organisms in general ward settings^[38]. From a financial perspective for instance, bloodstream infections caused by MDR organisms are estimated to increase treatment costs by 50%^[39]. What effect such local outbreaks of MDR bacteria have on process of care within a hospital setting and outwith is dependent on effective surveillance, and links between infection control, Public health, and health policy makers. This data is all too often insufficient or not translated into effective intervention.

ANTIBIOTIC STEWARDSHIP PROGRAMMES IN ICU

Antibiotic stewardship programmes (ASP) are regarded as a keystone in tackling AMR in ICU. The intention is to reduce antibiotic resistance by minimising selection pressure, through optimising antibiotic therapy^[40-44]. In Europe, the implementation

of ASP follows a “top-down” model, with European council recommendations (*i.e.*, the Prague framework) and national-level guidance (*e.g.*, The Scottish Management of Antimicrobial Resistance Action Plan, ScotMARAP) informing delivery programmes at critical care network and individual unit levels^[45,46]. In the context of these strategic initiatives, we have conducted the following systematic review of published ASPs in the ICU.

SUCCESS AND SHORTFALLS OF ASP IN THE ICU SETTING

Search strategy

To identify the eligible studies MEDLINE was searched from January 1996 to May 2014 using the following strategy: antibiotic and (stewardship programme or restriction or audit or decision support or education or guideline or policy or control or escalation or de-escalation) and (intensive care or critical care). The search was further refined by adding MeSH terms (intensive care unit or intensive care or critical care). Only human studies were included. The reference lists of all studies were reviewed to identify additional studies. Duplicate studies and conference abstracts were excluded.

Results

Forty three studies of ASPs in the ICU were identified. Thirty four were non-protocolised ASPs, and 9 studies of protocol-based ASPs. Their major findings are summarised in Table 1 and Table 2, respectively.

Out of the 34 non-protocolised ASPs, only 1 (3%) was a randomised controlled trial, whilst 22 (65%) were retrospective observational studies. Twenty nine (84%) studies comprised a single strategy, and 10 (29%) studies had a follow-up period of longer than one year. Antibiotic usage was the most common primary outcome measure (28 studies, 82%), followed by ICU LOS (19, 56%), mortality (15, 44%), antibiotic resistance (14, 41%) and antibiotics' cost (11, 32%). Twenty nine (85%) studies were regarded as positive studies, defined as achieving favourably in least one of the five aforementioned outcomes. Thirteen (38%) studies were conducted in specialist ICUs (purely medical, surgical, neonatal, paediatric or trauma). With respect to limitations, 8 (24%) had missing patient characteristics, whilst 4 (12%) studies had inconsistencies in patient characteristics between pre- and post-intervention arms.

Limitations of many of the non-protocolised ASP studies, particularly in regard to lack of consistency between the ASP and standard care arms are evident. Therefore, interpretation of the findings from these studies can at best be hypothesis-generating only. For instance, lack of standardised

Table 1 Non-protocolised antibiotic stewardship programmes

Kollef <i>et al</i> ^[18]	1997	9351601	Prospective cohort study Follow-up 6 mo	Incidence of VAP Incidence of bloodstream infection and sepsis Duration of mechanical ventilation LOS Mortality	680	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in resistant Gram negative organisms 3 ↓ in VAP incidence 4 No change to mortality 5 No change to LOS	1 No information on antibiotic usage 2 6 mo follow-up period only
Evans <i>et al</i> ^[19]	1998	9435330	Prospective observational study Follow-up 1 yr	Antibiotic use Antibiotic cost Cost of hospitalisation Number of adverse events caused by anti-infective agents No. of days of excessive antibiotic dosage LOS Mortality	1681	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↓ in total antibiotics cost 3 No change in DDD 4 ↓ in susceptibility-mismatch 5 ↓ in allergy-mismatch 6 ↓ of mortality 7 ↓ of LOS from 4.9 d to 2.7 d (4.9 to 8.3 d if overridden)	1 Less patients in post-intervention group 2 Young patients (mean age < 50 yr)
Price <i>et al</i> ^[84]	1999	10548192	Retrospective observational study Follow-up 1 mo	Antibiotic cost Antibiotic resistance LOS	321	Non-protocolised Components Antibiotic guideline	1 Positive study 2 77% ↓ in antibiotic cost 3 No change to LOS 4 No change to mortality	1 Surgical ICU only 2 1 mo FU follow-up 3 High compliance rate with guideline (95.6%) 4 High baseline APACHEII score (38.0-39.1)
Roger <i>et al</i> ^[64]	2000	11089498	Retrospective observational study Follow-up 2 mo	Antibiotic use Antibiotic cost	61	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ in duration of treatment from mean 23 d to 13 d 3 ↓ in total antibiotic days from 596 d to 455 d 4 19% ↓ in total antibiotic cost 5 No change to mortality 6 No change to LOS	1 2 mo follow-up period
Fox <i>et al</i> ^[63]	2001	11712090	Retrospective observational study Follow-up 1 yr	Antibiotic use LOS Days on mechanical ventilation Days with fever No. of cultures performed Antibiotic resistance Antibiotic cost	295	Non-protocolised Components ID specialist input	1 Negative study 2 No change to antibiotic usage 3 57% ↓ in antibiotics cost 4 ↑ infection rate 5 No change in LOS	1 Trauma ICU only 2 Young patients (age < 35 yr)
Mullett <i>et al</i> ^[90]	2001	11581483	Retrospective observational study Follow-up 6 mo	Antibiotic cost Rate of anti-infective sub-therapeutic and excessive-dose days	1758	Non-protocolised Components Computerised decision support tool	1 Negative study 2 No change to total cost of antibiotics 3 ↓ of excessive dose days and sub-therapeutic days (<i>i.e.</i> , dose optimisation)	1 Paediatric ICU only 2 Significantly younger patients in post-intervention group
Dos Santos <i>et al</i> ^[61]	2003	14552737	Retrospective observational study Follow-up 1 yr	Antibiotic use Antibiotic cost	1473	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ in cephalosporin, carbapenems and vancomycin usage 3 ↑ in penicillin usage 4 ↓ of cost by 37%	1 Limited patient characteristics 2 No information on antibiotic resistance 3 No information on LOS and mortality

Du <i>et al</i> ^[62]	2003	12682477	Prospective observational study Follow-up 1 yr	Antibiotic use Antibiotic resistance LOS	1205	Non-protocolised Components Antibiotic restriction Senior clinician input	1 Positive study 2 ↓ in 3 rd generation cephalosporin usage 3 ↑ in cefepime usage 4 No change to resistance pattern 5 ↓ in LOS from 13.1 d to 9.3 d	1 Significant reduction in APACHEII scores and organ failure % in post-intervention group 2 High baseline <i>Pseudomonas</i> and <i>Acinetobacter</i> rate 3 No information on mortality
Geissler <i>et al</i> ^[82]	2003	12528022	Retrospective observational study Follow-up 4 yr	Antibiotic use Antibiotic resistance Antibiotic cost	1704	Non-protocolised Components <i>Antibiotic guideline</i>	1 Positive study 2 35% ↓ in antibiotic days 3 37% ↓ in antibiotics cost 4 Significant ↓ in total number of resistant isolates	1 High baseline mortality 2 No data on LOS
Micek <i>et al</i> ^[81]	2004	15136392	RCT Follow-up 14 mo	Antibiotic use Incidence of VAP LOS Mortality	290	Non-protocolised Components Antibiotic discontinuation policy	1 Positive study 2 ↓ of antibiotic treatment duration 3 No change to LOS 4 No change to mortality	1 Medical ICU only 2 Limited microbiology data
Aubert <i>et al</i> ^[80]	2005	15620440	Retrospective observational study Follow-up 1 yr	Antibiotic use Microbiological profile and antibiotic resistance	781	Non-protocolised Components Antibiotic restriction	1 Positive study 2 ↓ in fluoroquinolone usage by 75.8% 3 ↓ in usage of aminoglycosides and macrolides 4 ↓ of antibiotic resistance in <i>Pseudomonas</i> 5 No change to mortality 6 No change to LOS	1 No information on antibiotic usage
Sintchenko <i>et al</i> ^[89]	2005	15802478	Prospective observational study Follow-up 6 mo	Antibiotic use LOS Mortality	5176 patient-days	Non-protocolised Components Computerised decision support tool	1 Positive study 2 Significant ↓ in total DDD from 1925 to 1606, particularly vancomycin and beta-lactam resistant penicillins 3 ↓ of mean LOS from 7.15 to 6.22 d 4 No change to mortality	1 6 mo follow-up period 2 No information on antibiotic resistance
Bochicchio <i>et al</i> ^[88]	2006	16500251	Randomised pilot study Follow-up 6 mo	Antibiotic decision accuracy	125	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↑ in decision accuracy (verified by ID specialists)	1 No information on antibiotic usage 2 No information on antibiotic resistance
Brahmi <i>et al</i> ^[78]	2006a	16944257	Retrospective observational study Follow-up 2 yr	Antibiotic use	727	Non-protocolised Components Antibiotic restriction	1 Positive study 2 Significant ↓ in ceftazidime usage 3 ↓ in tazocin and imipenem resistance 4 ↑ resistance to penicillins	1 High baseline rate of VAP patients (63%-70%) 2 High baseline resistance rate among <i>Pseudomonas</i> (59% to tazocin, 58% to ciprofloxacin, 58% to imipenem, 47% to ceftazidime) 3 No info on mortality and LOS
Thursky <i>et al</i> ^[87]	2006	16415039	Prospective observational study Follow-up 6 mo	Antibiotic use Antibiotic susceptibility-mismatches Mortality	1060	Non-protocolised Components Computerised decision support tool	1 Positive study 2 ↓ of total DDD from 1670 to 1490 3 ↓ in usage of ceftriaxone, vancomycin and carbapenems 4 ↓ of susceptibility-mismatch 5 No change to mortality	1 6 mo follow-up period 2 High baseline mortality (19%) 3 Fewer isolates in intervention group 4 No information on LOS

Brahmi <i>et al</i> ^[79]	2006b	17027213	Prospective cohort study Follow-up 2 yr	Antibiotic use Antibiotic resistance	318	Non-protocolised Components Antibiotic guideline	1 Positive study 2 ↓ in duration of treatment from 14.1 to 11.9 d 3 ↓ in antibiotics cost 4 ↓ in LOS from 20.4 to 16.9 d 5 No change to mortality	
de Araujo <i>et al</i> ^[69]	2007	17625777	Retrospective observational study Follow-up 1 yr	LOS Days of parenteral nutrition Requirement for mechanical ventilation Antibiotic use	995	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in cefepime usage 3 ↑ in tazocin usage 4 No change to LOS	1 Neonatal ICU only 2 High baseline rates of <i>Pseudomonas</i> and <i>Klebsiella</i> 3 No information on mortality
Ntagiopoulos <i>et al</i> ^[77]	2007	17629680	Retrospective observational study Follow-up 6 mo	Antibiotic use Antibiotic resistance	147	Non-protocolised Components Antibiotic restriction	1 Positive study 2 ↓ of overall antibiotic usage by 55% 3 ↓ in resistance in <i>Pseudomonas</i> 4 ↑ in resistant strains of <i>Klebsiella</i> and <i>Acinetobacter</i> 5 No change to mortality 6 No change to LOS	1 Male predominance 2 High baseline mortality 3 6 mo follow-up period 4 High baseline ceftazidime and fluoroquinolone resistance 5 90% policy compliance among clinicians
Ding <i>et al</i> ^[76]	2008	18493864	Retrospective observational study Follow-up 2 yr	Antibiotic use Rate of bacterial resistance	900	Non-protocolised Components Antibiotic guideline Staff education	1 Positive study 2 ↓ in usage of 3rd generation cephalosporin 3 ↑ in usage of beta-lactams 4 ↓ in antibiotics cost 5 No change to LOS	1 Paediatric ICU only 2 High baseline antibiotic utilisation (98.7% patients were on antibiotics) 3 High baseline resistance rate (> 60% to cefepime, for <i>E coli</i> and <i>Klebsiella</i> ; > 20% to cefepime and imipenem, for <i>Pseudomonas</i>) 4 No information on mortality
Peto <i>et al</i> ^[60]	2008	19011742	Retrospective observational study Follow-up 2 yr	Antibiotic use Incidence of sepsis LOS Mortality	3403	Non-protocolised Components Senior clinician input	1 Positive study 2 ↓ of mean DDD from 162.9 to 101.3. 3 No change to LOS 4 No change to mortality	1 Surgical ICU only with > 60% neurological patients 2 Low baseline resistance rate 3 Increased patient turnover since intervention
Marra <i>et al</i> ^[59]	2009	18986735	Retrospective observational study Follow-up 10 mo	Antibiotic resistance	360	Non-protocolised Components ID specialist input	1 Positive study 2 ↓ of total DDD by 12.1% 3 ↓ of resistant strains of <i>Pseudomonas</i> , <i>Klebsiella</i> and <i>Acinetobacter</i>	1 High baseline resistance rate 2 Limited patient characteristics 3 Unknown sample size 4 No information on mortality and LOS
Meyer <i>et al</i> ^[74]	2010	19904488	Retrospective observational study Follow-up 3 yr	Mortality Antibiotic use	11887	Non-protocolised Components Antibiotic prophylaxis	1 Positive study 2 15% ↓ in total antibiotic usage primarily cefuroxime and co-trimoxazole 3 Sustained ↓ to antibiotic usage 4 No change to LOS 5 No change to mortality	1 Surgical ICU only 2 Limited resistance data

Yong <i>et al</i> ^[86]	2010	20215130	Retrospective observational study Follow-up 4.5 yr	Antibiotic susceptibilities of <i>Pseudomonas</i> , <i>Klebsiella</i> , <i>Acinetobacter</i> and <i>Enterobacteriaceae</i>	13295	Non-protocolised Components Computerised decision support tool	1 Positive study 2 No change to Abx usage 3 ↑ susceptibility to imipenem for <i>Pseudomonas</i> , <i>Acinetobacter</i> and <i>Enterobacter</i> 4 ↑ susceptibility to gentamicin for <i>Pseudomonas</i> and <i>Enterobacter</i> 5 No change to LOS	1 Limited patient characteristics 2 No information on mortality
Sharma <i>et al</i> ^[75]	2010	21206622	Retrospective observational study Follow-up 4 mo	Antibiotic use Antibiotic resistance	177	Non-protocolised Components Antibiotic restriction	1 Negative study 2 ↓ of carbapenem usage 3 ↑ in beta-lactam usage	1 Medical ICU only 2 No information on overall antibiotic usage 3 4 mo follow-up period 4 No pre-intervention arm 5 Male predominance 6 High baseline <i>Acinetobacter</i> isolates 7 High baseline resistance rate
Raymond <i>et al</i> ^[68]	2011	11395583	Prospective cohort study Follow-up 1 yr	Mortality Duration of treatment Antibiotic cost LOS	1456	Non-protocolised Components Rotating antibiotic schedule	1 Positive study 2 ↓ in infection rate by 25% 3 ↓ in infections caused by resistant organisms 4 ↓ in usage of aminoglycosides, vancomycin and antifungals 5 ↑ in usage of clindamycin 6 ↓ in mortality from 38.1% to 15.5% 7 No change to LOS	1 No information on overall antibiotic usage 2 High baseline mortality rate
Dortch <i>et al</i> ^[67]	2011	21091186	Retrospective observational study Follow-up 8 yr	Incidence of infection caused by MDR organisms Antibiotic use	20846	Non-protocolised Components Antibiotic guidelines Antibiotic prophylaxis Rotating antibiotic schedules	1 Positive study 2 Significant ↓ of total broad spectrum antibiotic usage 3 ↓ in total infection rate 4 ↓ in MDR <i>Pseudomonas</i> , <i>Acinetobacter</i> and <i>Enterobacter</i> isolates	1 Surgical ICU only 2 High baseline respiratory infection rate 3 High baseline <i>Enterobacter</i> infection rate 4 Concomitant infection control policy
Slain <i>et al</i> ^[57]	2011	21687626	Retrospective observational study Follow-up 7 yr	Antibiotic use Antibiotic resistance	N/A	Non-protocolised Components Prospective audits Antibiotic restriction Staff education Antibiotic guidelines Rotating antibiotic schedules	1 Positive study 2 Overall ↓ of DDD 3 Fluctuations due to resistance and change in protocols 4 ↑ in resistance to ciprofloxacin, tazocin, cefepime	1 <i>Pseudomonas</i> infections only 2 Limited patient characteristics 3 No information on mortality or LOS

Chiu <i>et al</i> ^[73]	2011	21085051	Prospective observational study Follow-up 1 yr	Antibiotic use	190	Non-protocolised Components Antibiotic guideline	1 Negative study 2 No change to overall antibiotic usage 3 ↓ of vancomycin usage	1 Neonatal ICU only 2 Limited patient characteristics 3 Limited resistance data 4 No information on mortality and LOS
Sarraf-Yazdi <i>et al</i> ^[66]	2012	22445457	Retrospective observational study Follow-up 9 yr	Antibiotic use Antibiotic resistance	321	Non-protocolised Components Rotating antibiotic schedules	1 Positive study 2 No change in total antibiotic usage 3 ↓ in prescribed dosage of target antibiotics 4 ↓ in resistance against ceftazidime and tazocin	1 No LOS or mortality data 2 Limited patient characteristics
Sistanizad <i>et al</i> ^[72]	2013	24250656	Prospective cohort study Follow-up 9 mo	Antibiotic use Susceptibility of <i>P. aeruginosa</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> and <i>E. coli</i>	N/A	Non-protocolised Components Antibiotic restriction	1 Positive study 2. 60% ↓ in imipenem use 3 ↑ in carbapenem sensitivity for <i>Klebsiella</i> and <i>Pseudomonas</i>	1 No mortality and LOS data 2 Limited patient characteristic data
Rimavi <i>et al</i> ^[58]	2013	23873275	Prospective cohort study Follow-up 3 mo	Antimicrobial use Treatment duration APACHEII score LOS Mechanical ventilation days Mortality rate	246	Non-protocolised Components ID specialist input	1 Positive study 2 Significant ↓ in overall antibiotic usage 3 ↓ of LOS 4 No change to mortality	1 Medical ICU only 2 Follow-up period of only 3 mo 3 Limited resistance data
Bauer <i>et al</i> ^[71]	2013	23571547	Retrospective cohort study Follow-up N/A	Duration of mechanical ventilation LOS Mortality	1433	Non-protocolised Components Intermittent vs extended dosing regimen of cefipime	1 Positive study 2. ↓ of mortality from 20% to 3% 3 ↓ of LOS 4 ↓ of antibiotic cost per patient by \$23183 in extended dosing group	1 <i>Pseudomonas</i> infection only 2 No information on antibiotic resistance 3 No follow-up
Ramsamy <i>et al</i> ^[65]	2013	23725954	Retrospective observational study Follow-up 1 yr	Antibiotic use Antibiotic resistance	227	Non-protocolised Components Antibiotic restriction	1 Negative study 2 6.5% inappropriate broad-spectrum antibiotic usage	1 Trauma ICU 2 No pre-intervention arm 3 Limited patient characteristics 4 No information on mortality and LOS
Apisarnthanarak <i>et al</i> ^[98]	2014	24485368	Retrospective observational study Follow-up 1 yr	Rate of XDR <i>Acinetobacter baumannii</i> acquisition rate per 1000 patient days Rate of <i>Acinetobacter baumannii</i> infection or colonisation	1365	Not specified	1 Positive study 2 Significant ↓ in XDR <i>Acinetobacter baumannii</i> infection or colonisation rates	1 Type of ASP not specified 2 No information on antibiotic usage 3 Concomitant infection control policy (Use of disinfectant-detergent; Enhanced isolation; Active surveillance cultures for all ICU patients)

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHE II: Acute Physiology and Chronic Health Evaluation II.

antibiotic treatment initiation triggers to reduce inter-clinician decision tree variability, or inadvertent variations in clinico-biochemical information provided to both arms. Patient or antibiotic selection bias are a few such confounders.

All 9 protocol-based studies were randomised controlled trials, 4 (44%) being multi-centred. Eight

studies (89%) were procalcitonin-guided, and the remaining one (11%) was based on clinical scoring system. Only 1 (11%) study looked at the merit of PCT-guided ASP in both escalation and de-escalation of antibiotic treatment, whilst 5 (56%) and 3 (33%) studies, investigated its sole role in de-escalation or escalation, respectively. Six (67%) studies were

Table 2 Protocol-based antibiotic stewardship programmes

Ref.	Year	Pubmed ID	Study type	Outcome	No. of patients	Type of ASP	Major findings	Limitations/Confounding factors
Singh <i>et al.</i> ^[54]	2000	10934078	RCT Follow-up N/A	1 LOS 2 Mortality 3 Proportion of patients with resolution of pulmonary infiltrate	81	Clinical Pulmonary Infection Score-based De-escalation	1 Positive study 2 ↓ in total antibiotic days from 9.8 to 3 d 3 ↓ of antibiotics cost by \$381 per patient 4 ↓ in LOS from 14.7 to 9.4 d mean 5 Significant ↓ in total antibiotic resistance 6 No change to mortality	1 79% surgical patients 2 Mean APACHEII score of 42.7 in intervention group 3 Unknown follow-up period
Nobre <i>et al.</i> ^[47]	2008	18096708	Single-centred RCT	1 Anti-otic Antibiotic use 2 28-d mortality 3 LOS 4 Incidence of clinical cure 5 Recurrence of infection 6 Incidence of nosocomial superinfection	79	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from median 9.5 to 6 d 3 ↓ in ICU LOS from 5 to 3 d 4 ↓ in hospital LOS 21 to 14 d 5 No change to mortality	1 Small study 2 Sepsis patients only 6 Infections by <i>Pseudomonas</i> , <i>Acinetobacter</i> <i>etc.</i> were excluded 7 Patients with chronic infections were excluded 8 Immunocompromised patients were excluded 9 Patients on antibiotics at time of admission were excluded
Hochreiter <i>et al.</i> ^[48]	2009	19493352	Single-centred RCT	1 Antibiotic use 2 LOS 3 Mortality	110	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from median 7.9 to 5.9 d 3 ↓ in LOS from median 17.7 to 15.5 d 4 No change to mortality	1 Patients on antibiotics at time of admission were excluded 2 Sepsis patients only
Schroeder <i>et al.</i> ^[49]	2009	19034493	Single-centred RCT	1 Antibiotic use 2 LOS 3 Mortality	27	PCT-based De-escalation	1 Positive study 2 ↓ in duration of treatment from 8.3 to 6.6 d 3 ↓ in antibiotic cost by 17.8% 4 No change to LOS 5 No change to mortality	1 Sepsis patients only
Stolz <i>et al.</i> ^[55]	2009	19797133	Multi-centred RCT	1 No. of days without antibiotics at 28 d 2 Number of days without mechanical ventilation 3 ICU mortality 4 LOS 5 Incidence of VAP	101	PCT-based De-escalation	1 Positive study 2 27% ↓ in duration of treatment 3 No change to mortality 4 No change to LOS	1 VAP patients only
Bouadma <i>et al.</i> ^[50]	2010	20097417	Multi-centred RCT (PRORATA trial)	1 28-d and 60-d mortality 2 Number of days without antibiotics at 28 d 3 Incidence of recurrence of infection or superinfection 4 Days of unassisted breathing 5 LOS 6 Antibiotic use 7 Incidence of MDR organisms	630	PCT-based Escalation/ De-escalation	1 Positive study 2 ↓ in duration of treatment from 13.3 to 10.3 d 3 No change to mortality 4 No change to LOS	1 Patients on antibiotics on admission were excluded 2 Patients with chronic infection were excluded 3 Immunocompromised patients were excluded 4 90% medical patients 5 Close to 50% respiratory/CVS failure, and > 30% CNS failure 6 70% pulmonary infection site 7 53% did not adhere to algorithm in PCT group

Jensen <i>et al</i> ^[51]	2011	21572328	Multi-centred RCT (PASS trial)	1 28-d mortality	1200	PCT-based Treatment escalation	1 Negative study 2 Significant ↑ in duration of treatment (Median: from 4 to 6 d), especially for tazocin and meropenem 3 ↑ in LOS from median 5 to 6 d 4 No change to mortality	1 Low resistance and antibiotic usage units 2 Incomplete adherence to PCT algorithm
Layios <i>et al</i> ^[52]	2012	22809906	Single-centred RCT	1 Antibiotic use 2 Accuracy of infectious diagnosis 3 Diagnostic concordance between intensive care unit physician and ID specialist	510	VAP -based Escalation	1 Negative study 2 No change in duration of antibiotic treatment 3 No change in DDD 4 No change to LOS 5 No change in mortality	1 41% surgery and trauma patients
Annane <i>et al</i> ^[53]	2013	23418298	Multi-centred RCT	1 Proportion of patients on antibiotics at day 5	62	PCT-based Escalation	1 Negative study 2 Premature termination	1 Poor clinician compliance with algorithm 2 Patients on antibiotics at time of admission were excluded

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHEII: Acute Physiology and Chronic Health Evaluation II; PCT: Procalcitonin; CVS: Cardiovascular system; CNS: Central Nervous system; XDR: Extensively Drug-Resistant.

positive studies. The most commonly explored outcome measures were antibiotic usage (8 studies, 89%), ICU LOS (8 studies, 89%) and mortality (8 studies, 89%), followed by antibiotics' cost (2 studies, 22%) and antibiotic resistance (1 study, 11%). Clinician adherence was reported as a major issue in two (22%) studies.

In summary, 29 of 34 non-protocolised ASPs and 6 of 9 protocol-based ASPs were reported as positive studies. PCT guided prescribing, reduced antibiotic usage when used as a de-escalation/stop trigger^[47-49], and in one study using PCT for escalation/de-escalation^[50] It did not improve outcomes when used as an escalation trigger alone to reduce time-to-appropriate antibiotics^[51-53]. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection^[54,55]. No survival benefit in the ICU has yet been demonstrated.

Discussion

Four basic principles of ASP have been described: Timeliness, appropriateness, adequacy and duration of antibiotic usage^[56]. It represents a multifaceted approach that includes many components, and each individual ASP might encompass several, but not all, of them at a given time. These components include audits^[57], infectious disease specialist or senior clinician input^[58-64], or planned discontinuation/de-escalation of treatment in response to clinical and microbiological outcome data^[65]. Other components include rotating antibiotic schedules^[57,66-70] changes in prescribing policies involving antibiotic restriction, different dosing regimens or prophylaxis protocols^[57,62,65,67,71-84] and a multi-disciplinary

team (MDT) approach in treatment initiation and discontinuation, often emphasising feedback and non-punitive atmosphere among staff members^[83,85]. Some programmes also encompassed staff education^[57,74,76] and computerised decision support platforms^[86-91]. Concomitant regional or national infection control campaigns, for example in the United Kingdom between 2003 and 2008, might serve as necessary adjuvants to the success of ASPs.

Additional input comes from ICU-based pharmacy support^[92]. Pharmacists are significant drivers in ASPs, with roughly one-fifth of pharmacist intervention in an American trauma centre being ASP related^[93]. The MDT approach itself seems to be more effective than purely its components. In a prospective study of Antibiotic stewardship comparing an MDT approach with a non-MDT (involving only the infectious disease physician and ICU pharmacist), the former, which also includes other affiliated healthcare professionals, led to superior outcomes of appropriate antibiotic selection and the rates of antibiotic resistance^[94].

Protocol-based ASPs have recently gained popularity. Earlier programmes utilised clinical scoring systems in guiding antibiotic treatment^[54], whilst PCT-based ASPs are increasingly being adopted in ICUs. PCT is regarded as a superior biomarker of sepsis compared with many others discovered over the decades, including white cell count, C-reactive protein and interleukin-6. It is relatively unhindered by the issues of slow kinetics and non-specificity faced by the latter^[95-97]. Effective infection control and source control remain fundamental to successful ASPs^[98]. As has been demonstrated by the systematic review, there is a clear signal

suggesting the potential benefits of ASP, even in non protocolised observational studies. This of course depends on the outcome measured, but in regards decreased antibiotic duration, and cumulative prescribed burden, the results are favourable when PCT is used to guide antibiotic stop decisions. These reductions in antibiotic use have been verified in many PCT guided protocol based RCTs, but not as an antibiotic escalation trigger alone^[52,53,98]. Antibiotic reductions in these RCTs are demonstrated in the context of severe sepsis, critically ill surgical patients, single centre and multicentre trials, and in non microbiologically proven severe sepsis^[47-51,55]. Moreover concerns regarding increases in AMR have not been borne out. However, the potential for AMR selection through reduced dosing regimens remains possible. Further studies need a common minimum universal standards of antibiotic prescribing practice, that adopt pragmatic core principles, which are adapted to local circumstances.

UNANSWERED QUESTIONS AND PROSPECTS FOR FUTURE WORK

Antibiotic usage and resistance represent an increasing global concern. The latest figures from the United Kingdom reveal that hospital-acquired infection costs GBP 1 billion annually^[99], and USD 4.5 to 5.7 billions in the United States^[100]. It is unsurprising that commentaries refer to “crisis” and “catastrophe” when describing possible worst case scenarios of uncontrolled AMR. The wording from the 2014 WHO global report of such a post-antibiotic era emphasises the need for action to prevent such a time. To tackle this increasing challenge, one might envisage a combined approach involving the development of next generation antibiotics (significant development times and costs), new innovations such as nanotechnology in infection control^[101], together with strategies to optimise the effective use of currently available antimicrobials. Thus, ASPs involve a delicate interplay between economy, health and clinical evidence. To date the current high level evidence base for ASPs remains limited, with most of the reported studies being observational in nature. Those protocol based RCTs targeting de-escalation of antibiotics have demonstrated reduced usage, and on occasion reduced resistance patterns, length of stay but not manifested as survival benefit. Clinical decision support tools are of increasing interest in this regard.

Strategies to minimise antibiotic usage are multifaceted. It remains uncertain whether the reported success in literature with regard to ASPs could be attributed to ASP alone, or confounders such as concurrent infection control policies. Should an ASP not by implication require an effective infection

control policy? What would be the added value of the ASP? And what components should the ASP adopt? The role and impact of bed occupancy, staffing ratios and infection prevalence on antibiotic stewardship outcomes clearly require incorporation into study design. Further randomised controlled trials or indeed cluster studies, with staggered implementation of ASPs, where effective infection control policies are already in place may be required. Careful study design with appropriate components of the ASP, that could be implemented widely, would be desirable.

The dynamics of antibiotic resistance following the implementation of ASPs has been described as “balloon squeezing effect”^[102]. It is believed that the development of antibiotic resistance towards one class of antibiotics, could lead to the emergence of resistance against another class, rendering multi drug resistance. The molecular mechanisms behind this concept remain unclear. However, the use of quinolones for *Pseudomonas aeruginosa* may be relevant. Quinolones selectively upregulate the bacterial membrane efflux system MexEF-OprN, and the loss of co-regulated porin OprD results in carbapenem resistance^[103]. In a hypothetical situation where quinolones are routinely introduced empirically in favour of “targeted antibiotics” in a given ASP antibiotic regimen, resistance to both quinolones and carbapenems may develop.

Uncertainties around AMR in ICU being due to antibiotic selection pressure and distinguishing pathogenicity versus bystander effect of resistant organisms will remain a challenge for implementing fixed antibiotic protocols as part of ASPs. The lack of wholesale uptake of selective decontamination of the gut (SDD) or selective oral decontamination (SOD) to reduce rates of sepsis, is an example of this challenge^[104,105]. Despite high level evidence for their efficacy, uptake is poor^[106,107], with concerns regarding emergence of resistance being borne out in some settings^[108].

Further evidence of practical difficulties in implementation of ASPs is the recent RCT of a PCT-based ASP. This was terminated prematurely due to poor clinician adherence to the algorithm^[98]. Understanding the rationale behind clinician compliance and lack of it, specific to ASP antibiotic start and stop decisions will be important in designing future studies.

The culture positivity of microbiological isolates among ICU patients with suspected infections is generally low. EPIC II and SOAP studies reported culture positivity in only 51.4% and 60% of patients^[2,3]. Furthermore, time required to identify the causative organism far exceed the clinical decision time. Until such time as rapid diagnostics can confidently rule out suspected infection within minutes, and the knowledge that delayed or inappropriate antimicrobials in sepsis equates with

higher mortality, even PCT-guided ASPs might not prevent clinician decision tree analysis based upon opinion. Thus, studies investigating its role in treatment escalation yielded relative limited information to this date. The prospect of novel rapid identification tools to enhance ASP programmes is another crucial facet of ASP^[47]. The call here has been heeded, with the announcement of monetary prizes of up to \$17 million, and \$20 million from the NESTA foundation (a United Kingdom organisation through the Longitude prize 2014), and the United States NIH/Biomedical Advanced Research Authority^[7,109,110]. The US Administration also released its *National Strategy on Combating Antibiotic-Resistant Bacteria*. In addition, the President's Council of Advisors on Science and Technology (PCAST) is releasing a related report on *Combating Antibiotic Resistance*. The *National Strategy* provides a five-year plan for enhancing domestic and international capacity to prevent and contain outbreaks of antibiotic-resistant infections; maintain the efficacy of current and new antibiotics; and develop and deploy next-generation diagnostics, antibiotics, vaccines, and other therapeutics. The PCAST report provides recommendations from the President's Council and allied scientific and professional agencies, to act for the development of more effective ASPs^[7].

The costs associated with ASP, have so far been limited to those of the prescribed antibiotics. Nonetheless, costs related to staff employment and education, as well as management and information technology, will require necessary health economic analysis.

It is said that, where ASP is today, is infection control programmes thirty years ago^[111]. Thus the unanswered questions we encounter today might well hide the solution to the increasing burden of infection and AMR in ICUs and beyond. A multifaceted approach involving key stakeholders - healthcare, industry, technology, economy, security, government, charity and the public is warranted, to overcome AMR and perpetuate the future utility of antibiotics^[112]. Refined and tailored Antibiotic stewardship programmes in (and outwith) ICU will be an important part of that partnership.

REFERENCES

- 1 **Brusselsaers N**, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. *Ann Intensive Care* 2011; **1**: 47 [PMID: 22112929 DOI: 10.1186/2110-5820-1-47]
- 2 **Vincent JL**, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344-353 [PMID: 16424713 DOI: 10.1097/01.CCM.0000194725.48928.3A]
- 3 **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]
- 4 **Kumar A**, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589-1596 [PMID: 16625125 DOI: 10.1097/01.CCM.0000217961.75225.E9]
- 5 **Eggimann P**, Pittet D. Infection control in the ICU. *Chest* 2001; **120**: 2059-2093 [PMID: 11742943 DOI: 10.1378/chest.120.6.2059]
- 6 **Edbrooke DL**, Hibbert CL, Kingsley JM, Smith S, Bright NM, Quinn JM. The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care unit. *Crit Care Med* 1999; **27**: 1760-1767 [PMID: 10507595 DOI: 10.1097/00003246-199909000-00010]
- 7 **Office of the Press Secretary**, White House. FACT SHEET: Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria (2014). Available form: URL: <http://www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistance>
- 8 **World Health Organization**. Antimicrobial resistance global report on surveillance: 2014 summary. 2014. Available form: URL: http://www.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf
- 9 **National Nosocomial Infections Surveillance (NNIS) System Report**, Data Summary from January 1992-June 2001, issued August 2001. *Am J Infect Control* 2001; **29**: 404-421 [PMID: 11743489 DOI: 10.1067/mic.2001.119952]
- 10 **Hanberger H**, Arman D, Gill H, Jindrák V, Kalenic S, Kurcz A, Licker M, Naaber P, Scicluna EA, Vanis V, Walther SM. Surveillance of microbial resistance in European Intensive Care Units: a first report from the Care-ICU programme for improved infection control. *Intensive Care Med* 2009; **35**: 91-100 [PMID: 18670757 DOI: 10.1007/s00134-008-1237-y]
- 11 **ARSP Working Group**, The Sri Lanka College of Microbiologists. A multi centre laboratory study of Gram negative bacterial blood stream infections in Sri Lanka. *Ceylon Med J* 2013; **58**: 56-61 [PMID: 23817934 DOI: 10.4038/cmj.v58i2.5680]
- 12 **Johansson M**, Phuong DM, Walther SM, Hanberger H. Need for improved antimicrobial and infection control stewardship in Vietnamese intensive care units. *Trop Med Int Health* 2011; **16**: 737-743 [PMID: 21410602 DOI: 10.1111/j.1365-3156.2011.02753.x]
- 13 **Curcio DJ**. Antibiotic prescription in intensive care units in Latin America. *Rev Argent Microbiol* 2011; **43**: 203-211 [PMID: 22430995 DOI: 10.1590/S0325-75412011000300007]
- 14 **Saleem AF**, Qamar FN, Shahzad H, Qadir M, Zaidi AK. Trends in antibiotic susceptibility and incidence of late-onset Klebsiella pneumoniae neonatal sepsis over a six-year period in a neonatal intensive care unit in Karachi, Pakistan. *Int J Infect Dis* 2013; **17**: e961-e965 [PMID: 23759260 DOI: 10.1016/j.ijid.2013.04.007]
- 15 **National Research Council (US) Committee on Drug Use in Food Animals**. The Use of Drugs in Food Animals: Benefits and Risks. Washington (DC): National Academies Press (US), 1999
- 16 **Seiffert SN**, Hilty M, Perreten V, Endimiani A. Extended-spectrum cephalosporin-resistant Gram-negative organisms in livestock: an emerging problem for human health? *Drug Resist Updat* 2013; **16**: 22-45 [PMID: 23395305 DOI: 10.1016/j.drug.2012.12.001]
- 17 **Belmar Campos C**, Fenner I, Wiese N, Lensing C, Christner M, Rohde H, Aepfelbacher M, Fenner T, Hentschke M. Prevalence and genotypes of extended spectrum beta-lactamases in Enterobacteriaceae isolated from human stool and chicken meat in Hamburg, Germany. *Int J Med Microbiol* 2014; **304**: 678-684 [PMID: 24856867 DOI: 10.1016/j.ijmm.2014.04.012]
- 18 **Kollef MH**, Sharpless L, Vlasnik J, Pasque C, Murphy D, Fraser VJ. The impact of nosocomial infections on patient outcomes following cardiac surgery. *Chest* 1997; **112**: 666-675 [PMID: 9315799 DOI: 10.1378/chest.112.3.666]
- 19 **Richards MJ**, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med* 1999; **27**: 887-892 [PMID: 10362409 DOI: 10.1097/00003246-199905000-00020]

- 20 **Rahal JJ**, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, Mariano N, Marks S, Burns JM, Dominick D, Lim M. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. *JAMA* 1998; **280**: 1233-1237 [PMID: 9786372 DOI: 10.1001/jama.280.14.1233]
- 21 **Alfieri N**, Ramotar K, Armstrong P, Spornitz ME, Ross G, Winnick J, Cook DR. Two consecutive outbreaks of *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*) in an intensive-care unit defined by restriction fragment-length polymorphism typing. *Infect Control Hosp Epidemiol* 1999; **20**: 553-556 [PMID: 10466556 DOI: 10.1086/501668]
- 22 **Harbarth S**, Sudre P, Dharan S, Cadenas M, Pittet D. Outbreak of *Enterobacter cloacae* related to understaffing, overcrowding, and poor hygiene practices. *Infect Control Hosp Epidemiol* 1999; **20**: 598-603 [PMID: 10501256 DOI: 10.1086/501677]
- 23 **Haley RW**, Cushion NB, Tenover FC, Bannerman TL, Dryer D, Ross J, Sánchez PJ, Siegel JD. Eradication of endemic methicillin-resistant *Staphylococcus aureus* infections from a neonatal intensive care unit. *J Infect Dis* 1995; **171**: 614-624 [PMID: 7876608 DOI: 10.1093/infdis/171.3.614]
- 24 **Vicca AF**. Nursing staff workload as a determinant of methicillin-resistant *Staphylococcus aureus* spread in an adult intensive therapy unit. *J Hosp Infect* 1999; **43**: 109-113 [PMID: 10549310 DOI: 10.1053/jhin.1999.0246]
- 25 **Fridkin SK**, Pear SM, Williamson TH, Galgiani JN, Jarvis WR. The role of understaffing in central venous catheter-associated bloodstream infections. *Infect Control Hosp Epidemiol* 1996; **17**: 150-158 [PMID: 8708352 DOI: 10.2307/30142373]
- 26 **Vogelaers D**, De Bels D, Forêt F, Cran S, Gilbert E, Schoonheydt K, Blot S. Patterns of antimicrobial therapy in severe nosocomial infections: empiric choices, proportion of appropriate therapy, and adaptation rates—a multicentre, observational survey in critically ill patients. *Int J Antimicrob Agents* 2010; **35**: 375-381 [PMID: 20122817 DOI: 10.1016/j.ijantimicag.2009.11.015]
- 27 **Bonten MJ**, Bergmans DC, Speijer H, Stobberingh EE. Characteristics of polyclonal endemicity of *Pseudomonas aeruginosa* colonization in intensive care units. Implications for infection control. *Am J Respir Crit Care Med* 1999; **160**: 1212-1219 [PMID: 10508809 DOI: 10.1164/ajrcm.160.4.9809031]
- 28 **McKinnell JA**, Kunz DF, Chamot E, Patel M, Shirley RM, Moser SA, Baddley JW, Pappas PG, Miller LG. Association between vancomycin-resistant *Enterococci* bacteremia and ceftriaxone usage. *Infect Control Hosp Epidemiol* 2012; **33**: 718-724 [PMID: 22669234 DOI: 10.1086/666331]
- 29 **Rello J**, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest* 1993; **104**: 1230-1235 [PMID: 8404198 DOI: 10.1378/chest.104.4.1230]
- 30 **Kollef MH**. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993; **270**: 1965-1970 [PMID: 8411554 DOI: 10.1001/jama.1993.03510160083034]
- 31 **Edmond MB**, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, Wenzel RP. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin Infect Dis* 1995; **20**: 1126-1133 [PMID: 7619987 DOI: 10.1093/clinids/20.5.1126]
- 32 **Kollef MH**, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. *Chest* 1995; **108**: 1655-1662 [PMID: 7497777 DOI: 10.1378/chest.108.6.1655]
- 33 **Chastre J**, Wolff M, Fagon JY, Chevret S, Thomas F, Wernert D, Clementi E, Gonzalez J, Jussierand D, Asfar P, Perrin D, Fieux F, Aubas S. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003; **290**: 2588-2598 [PMID: 14625336 DOI: 10.1001/jama.290.19.2588]
- 34 **Jenkins TC**, Stella SA, Cervantes L, Knepper BC, Sabel AL, Price CS, Shockley L, Hanley ME, Mehler PS, Burman WJ. Targets for antibiotic and healthcare resource stewardship in inpatient community-acquired pneumonia: a comparison of management practices with National Guideline Recommendations. *Infection* 2013; **41**: 135-144 [PMID: 23160837 DOI: 10.1007/s15010-012-0362-2]
- 35 **Levy ER**, Swami S, Dubois SG, Wendt R, Banerjee R. Rates and appropriateness of antimicrobial prescribing at an academic children's hospital, 2007-2010. *Infect Control Hosp Epidemiol* 2012; **33**: 346-353 [PMID: 22418629 DOI: 10.1086/664761]
- 36 **Blot S**, Depuydt P, Vandewoude K, De Bacquer D. Measuring the impact of multidrug resistance in nosocomial infection. *Curr Opin Infect Dis* 2007; **20**: 391-396 [PMID: 17609598 DOI: 10.1097/QCO.0b013e32818be6f7]
- 37 **Salgado CD**, O'Grady N, Farr BM. Prevention and control of antimicrobial-resistant infections in intensive care patients. *Crit Care Med* 2005; **33**: 2373-2382 [PMID: 16215395 DOI: 10.1097/01.CCM.0000181727.04501.F3]
- 38 **Cosgrove SE**. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006; **42** Suppl 2: S82-S89 [PMID: 16355321 DOI: 10.1086/499406]
- 39 **Vandijck DM**, Depaemelaere M, Labeau SO, Depuydt PO, Annemans L, Buyle FM, Oeyen S, Colpaert KE, Peleman RP, Blot SI, Decruyenaere JM. Daily cost of antimicrobial therapy in patients with Intensive Care Unit-acquired, laboratory-confirmed bloodstream infection. *Int J Antimicrob Agents* 2008; **31**: 161-165 [PMID: 18164599 DOI: 10.1016/j.ijantimicag.2007.10.015]
- 40 **Deege MP**, Paterson DL. Reducing the development of antibiotic resistance in critical care units. *Curr Pharm Biotechnol* 2011; **12**: 2062-2069 [PMID: 22188438 DOI: 10.2174/138920111798808301]
- 41 **Gandhi TN**, DePestel DD, Collins CD, Nagel J, Washer LL. Managing antimicrobial resistance in intensive care units. *Crit Care Med* 2010; **38**: S315-S323 [PMID: 20647789 DOI: 10.1097/CCM.0b013e3181e6a2a4]
- 42 **De Angelis G**, Restuccia G, Cauda R, Tacconelli E. How could we reduce antibiotic use in critically ill patients? *Infect Disord Drug Targets* 2011; **11**: 376-383 [PMID: 21679144 DOI: 10.2174/18715261179650479]
- 43 **Piper GL**, Kaplan LJ. Antibiotic heterogeneity optimizes antimicrobial prescription and enables resistant pathogen control in the intensive care unit. *Surg Infect (Larchmt)* 2012; **13**: 194-202 [PMID: 22913313 DOI: 10.1089/sur.2012.121]
- 44 **Arnold HM**, Micek ST, Skrupky LP, Kollef MH. Antibiotic stewardship in the intensive care unit. *Semin Respir Crit Care Med* 2011; **32**: 215-227 [PMID: 21506058 DOI: 10.1055/s-0031-1275534]
- 45 **Bal AM**, Gould IM. Antibiotic stewardship: overcoming implementation barriers. *Curr Opin Infect Dis* 2011; **24**: 357-362 [PMID: 21587070 DOI: 10.1097/QCO.0b013e3283483262]
- 46 **Allerberger F**, Gareis R, Jindrák V, Struelens MJ. Antibiotic stewardship implementation in the EU: the way forward. *Expert Rev Anti Infect Ther* 2009; **7**: 1175-1183 [PMID: 19968511 DOI: 10.1586/eri.09.96]
- 47 **Nobre V**, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008; **177**: 498-505 [PMID: 18096708 DOI: 10.1164/rccm.200708-1238OC]
- 48 **Hochreiter M**, Köhler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care* 2009; **13**: R83 [PMID: 19493352 DOI: 10.1186/cc7903]
- 49 **Schroeder S**, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. *Langenbecks Arch Surg* 2009; **394**: 221-226 [PMID: 19034493 DOI: 10.1007/s00423-008-0432-1]
- 50 **Bouadma L**, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Régnier B, Brun-Buisson C, Chastre J, Wolff M. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; **375**: 463-474 [PMID: 20097417 DOI: 10.1016/S0140-6736(09)61879-1]
- 51 **Jensen JU**, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen

- MH, Thornberg KJ, Løken J, Steensen M, Fox Z, Tousi H, Sørensen P, Lauritsen AØ, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjær J, Grarup J, Lundgren JD. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med* 2011; **39**: 2048-2058 [PMID: 21572328 DOI: 10.1097/CCM.0b013e31821e8791]
- 52 **Layios N**, Lambermont B, Canivet JL, Morimont P, Preiser JC, Garweg C, Ledoux D, Frippiat F, Piret S, Giot JB, Wiesen P, Meuris C, Massion P, Leonard P, Nys M, Lancellotti P, Chapelle JP, Damas P. Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. *Crit Care Med* 2012; **40**: 2304-2309 [PMID: 22809906 DOI: 10.1097/CCM.0b013e318251517a]
- 53 **Annane D**, Maxime V, Faller JP, Mezher C, Clec'h C, Martel P, Gonzales H, Feissel M, Cohen Y, Capellier G, Gharbi M, Nardi O. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. *BMJ Open* 2013; **3**: e002186 [PMID: 23418298 DOI: 10.1136/bmjopen-2012-002186]
- 54 **Singh N**, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; **162**: 505-511 [PMID: 10934078 DOI: 10.1164/ajrcm.162.2.9909095]
- 55 **Stolz D**, Smyrniotou N, Eggimann P, Pargger H, Thakkar N, Siegemund M, Marsch A, Azzola A, Rakic J, Mueller B, Tamm M. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J* 2009; **34**: 1364-1375 [PMID: 19797133 DOI: 10.1183/09031936.00053209]
- 56 **Lawrence KL**, Kollef MH. Antimicrobial stewardship in the intensive care unit: advances and obstacles. *Am J Respir Crit Care Med* 2009; **179**: 434-438 [PMID: 19136370 DOI: 10.1164/rccm.200809-1394CP]
- 57 **Slain D**, Sarwari AR, Petros KO, McKnight RL, Sager RB, Mullett CJ, Wilson A, Thomas JG, Moffett K, Palmer HC, Dedhia HV. Impact of a Multimodal Antimicrobial Stewardship Program on *Pseudomonas aeruginosa* Susceptibility and Antimicrobial Use in the Intensive Care Unit Setting. *Crit Care Res Pract* 2011; **2011**: 416426 [PMID: 21687626 DOI: 10.1155/2011/416426]
- 58 **Rimawi RH**, Mazer MA, Siraj DS, Gooch M, Cook PP. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Crit Care Med* 2013; **41**: 2099-2107 [PMID: 23873275 DOI: 10.1097/CCM.0b013e31828e9863]
- 59 **Marra AR**, de Almeida SM, Correa L, Silva M, Martino MD, Silva CV, Cal RG, Edmond MB, dos Santos OF. The effect of limiting antimicrobial therapy duration on antimicrobial resistance in the critical care setting. *Am J Infect Control* 2009; **37**: 204-209 [PMID: 18986735 DOI: 10.1016/j.ajic.2008.06.008]
- 60 **Peto Z**, Benko R, Matuz M, Csullag E, Molnar A, Hajdu E. Results of a local antibiotic management program on antibiotic use in a tertiary intensive care unit in Hungary. *Infection* 2008; **36**: 560-564 [PMID: 19011742 DOI: 10.1007/s15010-008-7377-8]
- 61 **Dos Santos EF**, Silva AE, Pinhati HM, Maia Mde O. Effectiveness of the actions of antimicrobial control in the intensive care unit. *Braz J Infect Dis* 2003; **7**: 290-296 [PMID: 14552737 DOI: 10.1590/S1413-86702003000500002]
- 62 **Du B**, Chen D, Liu D, Long Y, Shi Y, Wang H, Rui X, Cui N. Restriction of third-generation cephalosporin use decreases infection-related mortality. *Crit Care Med* 2003; **31**: 1088-1093 [PMID: 12682477 DOI: 10.1097/01.CCM.0000059315.07526.DA]
- 63 **Fox BC**, Imrey PB, Voights MB, Norwood S. Infectious disease consultation and microbiologic surveillance for intensive care unit trauma patients: a pilot study. *Clin Infect Dis* 2001; **33**: 1981-1989 [PMID: 11712090 DOI: 10.1086/324083]
- 64 **Roger PM**, Hyvernat H, Verleine-Pugliese S, Bourroul C, Giordano J, Fosse T, Mousnier A, Dellamonica P, Mattéi M, Bernardin G. Systematic infection consultation in the intensive care unit. Impact of short-term antibiotic use. *Presse Med* 2000; **29**: 1640-1644 [PMID: 11089498]
- 65 **Ramsamy Y**, Muckart DJ, Han KS. Microbiological surveillance and antimicrobial stewardship minimise the need for ultrabroad-spectrum combination therapy for treatment of nosocomial infections in a trauma intensive care unit: an audit of an evidence-based empiric antimicrobial policy. *S Afr Med J* 2013; **103**: 371-376 [PMID: 23725954 DOI: 10.7196/samj.6459]
- 66 **Sarraf-Yazdi S**, Sharpe M, Bennett KM, Dotson TL, Anderson DJ, Vaslef SN. A 9-Year retrospective review of antibiotic cycling in a surgical intensive care unit. *J Surg Res* 2012; **176**: e73-e78 [PMID: 22445457 DOI: 10.1016/j.jss.2011.12.014]
- 67 **Dortch MJ**, Fleming SB, Kauffmann RM, Dossett LA, Talbot TR, May AK. Infection reduction strategies including antibiotic stewardship protocols in surgical and trauma intensive care units are associated with reduced resistant gram-negative healthcare-associated infections. *Surg Infect (Larchmt)* 2011; **12**: 15-25 [PMID: 21091186 DOI: 10.1089/sur.2009.059]
- 68 **Raymond DP**, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, Sawyer RG. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med* 2001; **29**: 1101-1108 [PMID: 11395583 DOI: 10.1097/00003246-200106000-00001]
- 69 **de Araujo OR**, da Silva DC, Diegues AR, Arkader R, Cabral EA, Afonso MR, Louzada ME, Albertoni Ade C. Cefepime restriction improves gram-negative overall resistance patterns in neonatal intensive care unit. *Braz J Infect Dis* 2007; **11**: 277-280 [PMID: 17625777 DOI: 10.1590/S1413-86702007000200022]
- 70 **Kollef MH**, Vlasnik J, Sharpless L, Pasque C, Murphy D, Fraser V. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1997; **156**: 1040-1048 [PMID: 9351601 DOI: 10.1164/ajrcm.156.4.9701046]
- 71 **Bauer KA**, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infections. *Antimicrob Agents Chemother* 2013; **57**: 2907-2912 [PMID: 23571547 DOI: 10.1128/AAC.02365-12]
- 72 **Sistanizad M**, Koucheh M, Miri M, Goharani R, Solouki M, Ayazkhoo L, Foroumand M, Mokhtari M. Carbapenem Restriction and its Effect on Bacterial Resistance in an Intensive Care unit of a Teaching Hospital. *Iran J Pharm Res* 2013; **12**: 503-509 [PMID: 24250656]
- 73 **Chiu CH**, Michelow IC, Cronin J, Ringer SA, Ferris TG, Puopolo KM. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *Pediatr Infect Dis J* 2011; **30**: 273-278 [PMID: 21085051 DOI: 10.1097/INF.0b013e3182011d12]
- 74 **Meyer E**, Schwab F, Pollitt A, Bettolo W, Schroeren-Boersch B, Trautmann M. Impact of a change in antibiotic prophylaxis on total antibiotic use in a surgical intensive care unit. *Infection* 2010; **38**: 19-24 [PMID: 19904488 DOI: 10.1007/s15010-009-9115-2]
- 75 **Sharma PR**, Barman P. Antimicrobial consumption and impact of "Reserve antibiotic indent form" in an intensive care unit. *Indian J Pharmacol* 2010; **42**: 297-300 [PMID: 21206622 DOI: 10.4103/0253-7613.70216]
- 76 **Ding H**, Yang Y, Wei J, Fan S, Yu S, Yao K, Wang A, Shen X. Influencing the use of antibiotics in a Chinese pediatric intensive care unit. *Pharm World Sci* 2008; **30**: 787-793 [PMID: 18493864 DOI: 10.1007/s11096-008-9220-9]
- 77 **Ntagiopoulos PG**, Paramythiotou E, Antoniadou A, Giamarellou H, Karabinis A. Impact of an antibiotic restriction policy on the antibiotic resistance patterns of Gram-negative microorganisms in an Intensive Care Unit in Greece. *Int J Antimicrob Agents* 2007; **30**: 360-365 [PMID: 17629680 DOI: 10.1016/j.ijantimicag.2007.05.012]
- 78 **Brahmi N**, Blel Y, Kouraichi N, Lahdhiri S, Thabet H, Hedhili A, Amamou M. Impact of ceftazidime restriction on gram-negative bacterial resistance in an intensive care unit. *J Infect Chemother* 2006; **12**: 190-194 [PMID: 16944257 DOI: 10.1007/s10156-006-0452-0]
- 79 **Brahmi N**, Blel Y, Kouraichi N, Ben Hamouda R, Thabet H, Amamou M. [Impact of antibiotic use and prescribing policy in a Tunisian intensive care unit]. *Med Mal Infect* 2006; **36**: 460-465 [PMID: 17027213 DOI: 10.1016/j.medmal.2006.07.012]

- 80 **Aubert G**, Carricajo A, Vautrin AC, Guyomarc'h S, Fonsale N, Page D, Brunel P, Rusch P, Zéni F. Impact of restricting fluoroquinolone prescription on bacterial resistance in an intensive care unit. *J Hosp Infect* 2005; **59**: 83-89 [PMID: 15620440 DOI: 10.1016/j.jhin.2004.07.016]
- 81 **Micek ST**, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004; **125**: 1791-1799 [PMID: 15136392 DOI: 10.1378/chest.125.5.1791]
- 82 **Geissler A**, Gerbeaux P, Granier I, Blanc P, Facon K, Durand-Gasselin J. Rational use of antibiotics in the intensive care unit: impact on microbial resistance and costs. *Intensive Care Med* 2003; **29**: 49-54 [PMID: 12528022]
- 83 **Lawton RM**, Fridkin SK, Gaynes RP, McGowan JE. Practices to improve antimicrobial use at 47 US hospitals: the status of the 1997 SHEA/IDSA position paper recommendations. Society for Healthcare Epidemiology of America/Infectious Diseases Society of America. *Infect Control Hosp Epidemiol* 2000; **21**: 256-259 [PMID: 10782587 DOI: 10.1086/501754]
- 84 **Price J**, Ekleberry A, Grover A, Melendy S, Baddam K, McMahon J, Villalba M, Johnson M, Zervos MJ. Evaluation of clinical practice guidelines on outcome of infection in patients in the surgical intensive care unit. *Crit Care Med* 1999; **27**: 2118-2124 [PMID: 10548192 DOI: 10.1097/00003246-199910000-00007]
- 85 **Patel SJ**, Saiman L, Duchon JM, Evans D, Ferng YH, Larson E. Development of an antimicrobial stewardship intervention using a model of actionable feedback. *Interdiscip Perspect Infect Dis* 2012; **2012**: 150367 [PMID: 22500166 DOI: 10.1155/2012/150367]
- 86 **Yong MK**, Buising KL, Cheng AC, Thursky KA. Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. *J Antimicrob Chemother* 2010; **65**: 1062-1069 [PMID: 20215130 DOI: 10.1093/jac/dkq058]
- 87 **Thursky KA**, Buising KL, Bak N, Macgregor L, Street AC, Macintyre CR, Presneill JJ, Cade JF, Brown GV. Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. *Int J Qual Health Care* 2006; **18**: 224-231 [PMID: 16415039 DOI: 10.1093/intqhc/mzi095]
- 88 **Bochicchio GV**, Smit PA, Moore R, Bochicchio K, Auwaerter P, Johnson SB, Scalea T, Bartlett JG. Pilot study of a web-based antibiotic decision management guide. *J Am Coll Surg* 2006; **202**: 459-467 [PMID: 16500251 DOI: 10.1016/j.jamcollsurg.2005.11.010]
- 89 **Sintchenko V**, Iredell JR, Gilbert GL, Coiera E. Handheld computer-based decision support reduces patient length of stay and antibiotic prescribing in critical care. *J Am Med Inform Assoc* 2005; **12**: 398-402 [PMID: 15802478 DOI: 10.1197/jamia.M1798]
- 90 **Mullett CJ**, Evans RS, Christenson JC, Dean JM. Development and impact of a computerized pediatric anti-infective decision support program. *Pediatrics* 2001; **108**: E75 [PMID: 11581483 DOI: 10.1542/peds.108.4.e75]
- 91 **Evans RS**, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, Lloyd JF, Burke JP. A computer-assisted management program for antibiotics and other anti-infective agents. *N Engl J Med* 1998; **338**: 232-238 [PMID: 9435330 DOI: 10.1056/NEJM199801223380406]
- 92 **Maechler F**, Schwab F, Geffers C, Meyer E, Leistner R, Gastmeier P. Antibiotic stewardship in Germany: a cross-sectional questionnaire survey of 355 intensive care units. *Infection* 2014; **42**: 119-125 [PMID: 24135909 DOI: 10.1007/s15010-013-0531-y]
- 93 **Hamblin S**, Rumbaugh K, Miller R. Prevention of adverse drug events and cost savings associated with PharmD interventions in an academic Level I trauma center: an evidence-based approach. *J Trauma Acute Care Surg* 2012; **73**: 1484-1490 [PMID: 23064610 DOI: 10.1097/TA.0b013e318267cd80]
- 94 **DiazGranados CA**. Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. *Am J Infect Control* 2012; **40**: 526-529 [PMID: 21937145 DOI: 10.1016/j.ajic.2011.07.011]
- 95 **Uzzan B**, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med* 2006; **34**: 1996-2003 [PMID: 16715031 DOI: 10.1097/01.CCM.0000226413.54364.36]
- 96 **Simon L**, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; **39**: 206-217 [PMID: 15307030 DOI: 10.1086/421997]
- 97 **Meisner M**, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. *Crit Care* 1999; **3**: 45-50 [PMID: 11056723 DOI: 10.1186/cc306]
- 98 **Apisarnthanarak A**, Pinitchai U, Warachan B, Warren DK, Khawcharoenporn T, Hayden MK. Effectiveness of infection prevention measures featuring advanced source control and environmental cleaning to limit transmission of extremely-drug resistant *Acinetobacter baumannii* in a Thai intensive care unit: An analysis before and after extensive flooding. *Am J Infect Control* 2014; **42**: 116-121 [PMID: 24485368 DOI: 10.1016/j.ajic.2013.09.025]
- 99 **National Audit Office**. Improving patient care by reducing the risk of hospital acquired infection: A progress report. London: The Stationary Office, 2004. Available form: URL: <http://www.nao.org.uk/wp-content/uploads/2004/07/0304876.pdf>
- 100 **Burke JP**. Infection control - a problem for patient safety. *N Engl J Med* 2003; **348**: 651-656 [PMID: 12584377 DOI: 10.1056/NEJMp020557]
- 101 **Singh R**, Smitha MS, Singh SP. The role of nanotechnology in combating multi-drug resistant bacteria. *J Nanosci Nanotechnol* 2014; **14**: 4745-4756 [PMID: 24757944 DOI: 10.1166/jnn.2014.9527]
- 102 **Peterson LR**. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. *Clin Microbiol Infect* 2005; **11** Suppl 5: 4-16 [PMID: 16138814 DOI: 10.1111/j.1469-0691.2005.01238.x]
- 103 **Livermore DM**. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis* 2002; **34**: 634-640 [PMID: 11823954]
- 104 **Daneman N**, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13**: 328-341 [PMID: 23352693 DOI: 10.1016/S1473-3099(12)70322-5]
- 105 **Liberati A**, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Syst Rev* 2009; **(4)**: CD000022 [PMID: 19821262 DOI: 10.1002/14651858.CD000022]
- 106 **Price R**, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ* 2014; **348**: g2197 [PMID: 24687313 DOI: 10.1136/bmj.g2197]
- 107 **Jongerden IP**, de Smet AM, Kluytmans JA, te Velde LF, Dennesen PJ, Wesselink RM, Bouw MP, Spanjersberg R, Bogaers-Hofman D, van der Meer NJ, de Vries JW, Kaasjager K, van Iterson M, Kluge GH, van der Werf TS, Harinck HI, Bindels AJ, Pickkers P, Bonten MJ. Physicians' and nurses' opinions on selective decontamination of the digestive tract and selective oropharyngeal decontamination: a survey. *Crit Care* 2010; **14**: R132 [PMID: 20626848 DOI: 10.1186/cc9180]
- 108 **Brink AJ**, Coetzee J, Corcoran C, Clay CG, Hari-Makkan D, Jacobson RK, Richards GA, Feldman C, Nutt L, van Greune J, Deetlefs JD, Swart K, Devenish L, Poirel L, Nordmann P. Emergence of OXA-48 and OXA-181 carbapenemases among Enterobacteriaceae in South Africa and evidence of in vivo selection of colistin resistance as a consequence of selective decontamination of the gastrointestinal tract. *J Clin Microbiol* 2013; **51**: 369-372 [PMID: 23152549 DOI: 10.1128/JCM.02234-12]
- 109 **NESTA**. British public votes to solve antibiotics challenge. Available form: URL: <http://www.nesta.org.uk/blog/british-public-votes-solve-antibiotics-challenge#sthash.uQgChxgF.dpuf>
- 110 **Longitude Prize** 2014. Available form: URL: <http://www.longitude-prize.org>

- 111 **George P**, Morris AM. Pro/con debate: Should antimicrobial stewardship programs be adopted universally in the intensive care unit? *Crit Care* 2010; **14**: 205 [PMID: 20236505 DOI: 10.1186/cc8219]
- 112 **Nathan C**, Cars O. Antibiotic resistance--problems, progress, and prospects. *N Engl J Med* 2014; **371**: 1761-1763 [PMID: 25271470 DOI: 10.1056/NEJMp1408040]

P- Reviewer: Cattermole G, Sertoglu E **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Wu HL



Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014

Jan Jacques Michiels, Janneke Maria Michiels, Wim Moossdorff, Mildred Lao, Hanny Maasland, Gualtiero Palareti

Jan Jacques Michiels, Wim Moossdorff, Mildred Lao, Hanny Maasland, Primary Care Medicine Medical Diagnostic Center, Vlambloem 21, 3068 JE Rotterdam, The Netherlands

Jan Jacques Michiels, Janneke Maria Michiels, Multidisciplinary Internist and Investigator, Goodheart Institute, Bloodcoagulation and Vascular Medicine Science Center Rotterdam, 3069 AT Rotterdam, The Netherlands

Jan Jacques Michiels, Gualtiero Palareti, Central European Vascular Forum, 11000 Prague, Czech

Janneke Maria Michiels, Primary Care Medicine, Leiden University Medical Center, Leiden, 2333 ZA Leiden, The Netherlands

Gualtiero Palareti, Department of Angiology and Blood Coagulation University Hospital, Policlinico S. Orsola-Malpighi, 40016 Bologna, Italy

Author contributions: Michiels JJ, Moossdorff W and Palareti G designed the study; Michiels JJ wrote the manuscript; Moossdorff W, Lao M and Maasland H performed the ultrasound studies; Michiels JM interpreted the results for use by family doctors.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Jan Jacques Michiels, MD, PhD, Professor, Multidisciplinary Internist and Investigator, Goodheart Institute, Bloodcoagulation and Vascular Medicine Research Center, Erasmus Tower, Veenmos 13, 3069 AT Rotterdam, The Netherlands. goodheartcenter@upcmail.nl

Telephone: +31-62-6970534

Received: March 11, 2014

Peer-review started: October 10, 2014

First decision: October 11, 2014

Revised: October 11, 2014

Accepted: November 7, 2014

Article in press: November 10, 2014

Published online: February 4, 2015

Abstract

The requirement for a safe diagnostic strategy of deep vein thrombosis (DVT) should be based on an overall objective post incidence of venous thromboembolism (VTE) of less than 1% during 3 mo follow-up. Compression ultrasonography (CUS) of the leg veins has a negative predictive value (NPV) of 97%-98% indicating the need of repeated CUS testing within one week. A negative ELISA VIDAS safely excludes DVT and VTE with a NPV between 99% and 100% at a low clinical score of zero. The combination of low clinical score and a less sensitive D-dimer test (Simplify) is not sensitive enough to exclude DVT and VTE in routine daily practice. From prospective clinical research studies it may be concluded that complete recanalization within 3-6 mo and no reflux is associated with a low or no risk of PTS obviating the need of MECS 6 mo after DVT. Partial and complete recanalization after 6 to more than 12 mo is usually complicated by reflux due to valve destruction and symptomatic PTS. Reflux seems to be a main determinant for PTS and DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT = partial recanalization) and the risk of VTE recurrence in prospective studies. Absence of RVT at 3 mo post-DVT and no reflux is predicted to be associated with no recurrence of DVT (1.2%) during follow-up obviating the need of wearing medical elastic stockings and anticoagulation at 6 mo post-DVT. The presence or absence of RVT but with reflux at or after 6 mo post-DVT is associated with both symptomatic PTS and an increased risk of VTE recurrence in about one third in the post-DVT period after regular discontinuation of anticoagulant treatment. To test this hypothesis we designed a prospective DVT and postthrombotic syndrome (PTS) Bridging the Gap Study by addressing at least four unanswered questions in the treatment of

DVT and PTS. Which DVT patient has a clear indication for long-term compression stocking therapy to prevent PTS after the initial anticoagulant treatment in the acute phase of DVT? Is 6 mo the appropriate point in time to determine candidates at risk to develop DVT recurrence and PTS? Which high risk symptomatic PTS patients need extended anticoagulant treatment?

Key words: Deep Venous thrombosis; Ultrasonography; Post-thrombotic syndrome; ELISA VIDAS D-dimer; Medical elastic stockings; Anticoagulation

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: A novel clinical concept for the assessment of acute deep vein thrombosis (DVT) and the post-thrombotic syndrome (PTS) by DUS in routine clinical practice at 1, 3 to 6 mo and at one year post-DVT will separate post-DVT patients in 4 groups: Group 1: rapid complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and medical elastic compression stockings (MECS) can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

Michiels JJ, Michiels JM, Moossdorff W, Lao M, Maasland H, Palareti G. Diagnosis of deep vein thrombosis, and prevention of deep vein thrombosis recurrence and the post-thrombotic syndrome in the primary care medicine setting anno 2014. *World J Crit Care Med* 2015; 4(1): 29-39 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/29.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.29>

DEEP-VEIN THROMBOSIS

The sequential use of compression ultrasonography (CUS), a sensitive ELISA VIDAS D-dimer test and clinical score to rule in and out deep vein thrombosis (DVT) and alternative diagnosis (AD) is safe and cost-effective (Figure 1)^[1-10]. The general application of DVT exclusion by a negative SimpliRed (Simplify) by the combination of a negative CUS and low clinical score is not safe enough^[5,9]. After a first negative CUS the prevalence of DVT is uniformly low, 2%-3%^[8,9-14]. The combination of a first negative CUS and a D-dimer level of ELISA VIDAS < 1000, Tina-quant < 800 µg/mL or negative SimpliRed (Simplify) will exclude deep vein thrombosis with a NPV of more than 99% in 4 prospective outcome

studies (Figure 1)^[9,11-13]. A moderate to high probability in combination with a increased ELISA D-dimer (VIDAS > 1000 or Tinaquant > 800 µg/mL) or a positive qualitative D-dimer (SimpliRed or Simplify) should be followed by a second CUS of the legs after one week^[12,13] to detect a thrombus in about 3% of patients (Figure 1)^[8,9,11-14].

DEEP VEIN THROMBOSIS AND THE POST-THROMBOTIC SYNDROME

Recanalization of distal DVT is usually rapid and complete within one to three months without reflux and no or low risk of post-thrombotic syndrome (PTS) in an asymptomatic leg obviating the need to extend anticoagulation at 6 mo post-DVT. Recanalization of proximal DVT is usually delayed and may be completed after 3, 6 to 9 mo post-DVT with a high incidence of reflux, DVT recurrence and PTS (Figure 2)^[15-17]. Loss of valve competence leading to ambulatory venous hypertension (AVP) and diversion of venous flow through incompetent perforans veins appear to play an important role in the development of late complications of the post-thrombotic syndrome (PTS)^[15,16]. Anatomic studies have described the most distribution of venous valves to be a single valve in the common femoral vein (CFV) above the sapheno-femoral junction, a relatively constant deep valve just before its termination in the CFV, three to four valves in the superficial femoral vein with relatively constant locations at the mid-thigh and adductor canal, one or two valves in the popliteal vein (PPV) and one to two valves with the terminal 2-2 cm of the greater saphenous vein (GSV). Among the calf veins, the PPV appears to be of primary importance in the development of the post-thrombotic syndrome, by virtue of both its importance in the calf muscle pump and its communications with the posterior arch vein. Meissner *et al*^[15] studied the relationship between complete recanalization (lysis time) and the development of reflux in patients with a first episode of DVT at 3 mo interval during the first year (Figure 2). Duplex criteria for complete occlusion were defined as the absence of detectable flow, either spontaneous or with augmentation, in an incompressible venous segment. Partial occlusion was defined as normal or diminished flow either spontaneous or with augmentation, in an incompletely compressible venous segment. Complete lysis of the leg vein clot (recanalization) was presumed to have occurred when spontaneous phasic flow returned and the vein was completely compressible^[15]. For the PTVs, flow detected after distal augmentation in a completely compressible vein is accepted as evidence of complete recanalization (lysis of the leg vein clot). The median time from DVT to complete recanalization (lysis

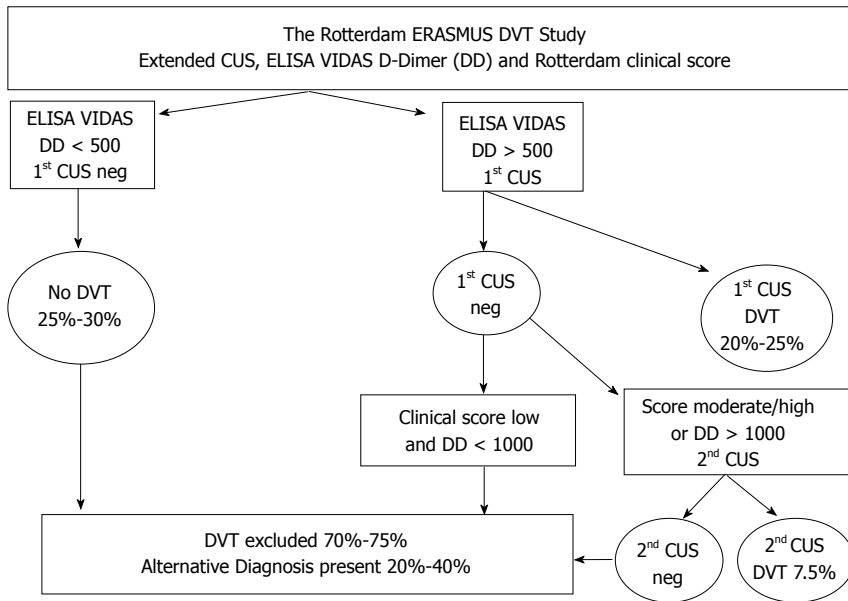


Figure 1 Rotterdam approach to safely exclude and diagnose deep vein thrombosis^[8,9]. CUS: Compression ultrasonography; DVT: Deep vein thrombosis.

Table 1 Scoring system according to Brandjes for mild-to-moderate and severe postthrombotic syndrome^[24]

Subjective criteria			
Symptoms	Score	Signs	Score
For mild-to-moderate PTS: score > 3 of subjective and objective criteria			
Spontaneous pain in calf	1	Calf circumference ↑ by 1 cm	1
Spontaneous pain in thigh	1	Ankle circumference ↑ by 1 cm	1
Calf pain on standing/walking	1	Pigmentation	1
Thigh pain on standing/walking	1	Venectasia	1
Edema of foot/calf	1	Newly formed varicosis	1
Heaviness of foot/leg	1	Phlebitis	1
For severe PTS score > 4 of symptoms and signs			
Spontaneous pain	1	Calf circumference ↑ by 1 cm	1
Pain on standing/walking	1	Pigmentation, discolouration, and venectasia	1
Edema calf	1		
Impairment of daily activities	4	Healed or active ulcer	1

time) was about 3 mo (100 d) for patients without reflux in all segments (Figure 2). In contrast, the median time from DVT to complete recanalization (lysis time) of all segments was about 9 to 12 mo (more than 6 mo) for DVT patients who developed reflux as the main determinant of PTS (Figure 2). In the study of 123 legs with DVT (107 patients) by Markel *et al.*^[16] about two third of the involved legs had developed valve incompetence. The distribution of reflux at the end of the first year follow-up in this study was the following: popliteal vein, 58%, superficial femoral vein, 37%, greater saphenous vein, 25% and posterior popliteal vein, 18%. Reflux appeared to be more frequent in the segments previously affected by DVT^[16].

From these two prospective clinical research studies^[15,16] it may be concluded that complete recanalization within 3 mo and no reflux is associated with a low or no risk of PTS obviating the need of medical elastic compression stockings (MECS) 6 mo after DVT (Table 1). On the other hand, partial and complete recanalization after 6-12 mo is usually complicated by reflux due to valve destruction. Consequently, reflux seems to be a main determinant for PTS and DVT recurrence, the latter as a main contributing factor in worsening PTS. This hypothesis is supported by the relation between the persistent residual vein thrombosis (RVT = partial recanalization) and the risk of VTE recurrence in two prospective studies^[18,19]. In a prospective outcome study, RVT at 3 mo post-DVT was absent in 30%, which was associated with low recurrence of DVT (1.2% patient/years) during two years follow-up (Table 2, Figure 3)^[18]. The presence of RVT at 3 mo post-DVT was associated with a DVT recurrence rate of 27% during two years follow-up after discontinuation of anticoagulant treatment (Table 2, Figure 3)^[18]. The proportion of provoked vs unprovoked DVT was 64% and 36% in patients with complete recanalization within 3 mo and 23% vs 77% in the patient with RVT (incomplete recanalization) at 3 mo post-DVT indicating that the distinction provoked vs unprovoked DVT is artificial in terms of risk on DVT recurrence.

In a previous prospective study of 313 consecutive DVT patients, Prandoni *et al.*^[19] have shown that RVT at any time post-DVT is a risk factor for recurrent VTE. In this study, CUS of the common femoral and popliteal veins was performed at 3, 6, 12, 24 and 36 mo post DVT. The cumulative incidence of normal CUS (no RVT) was 39%, 58%, 69% and 74% at 6, 12, 24 and 36 mo post DVT respectively.

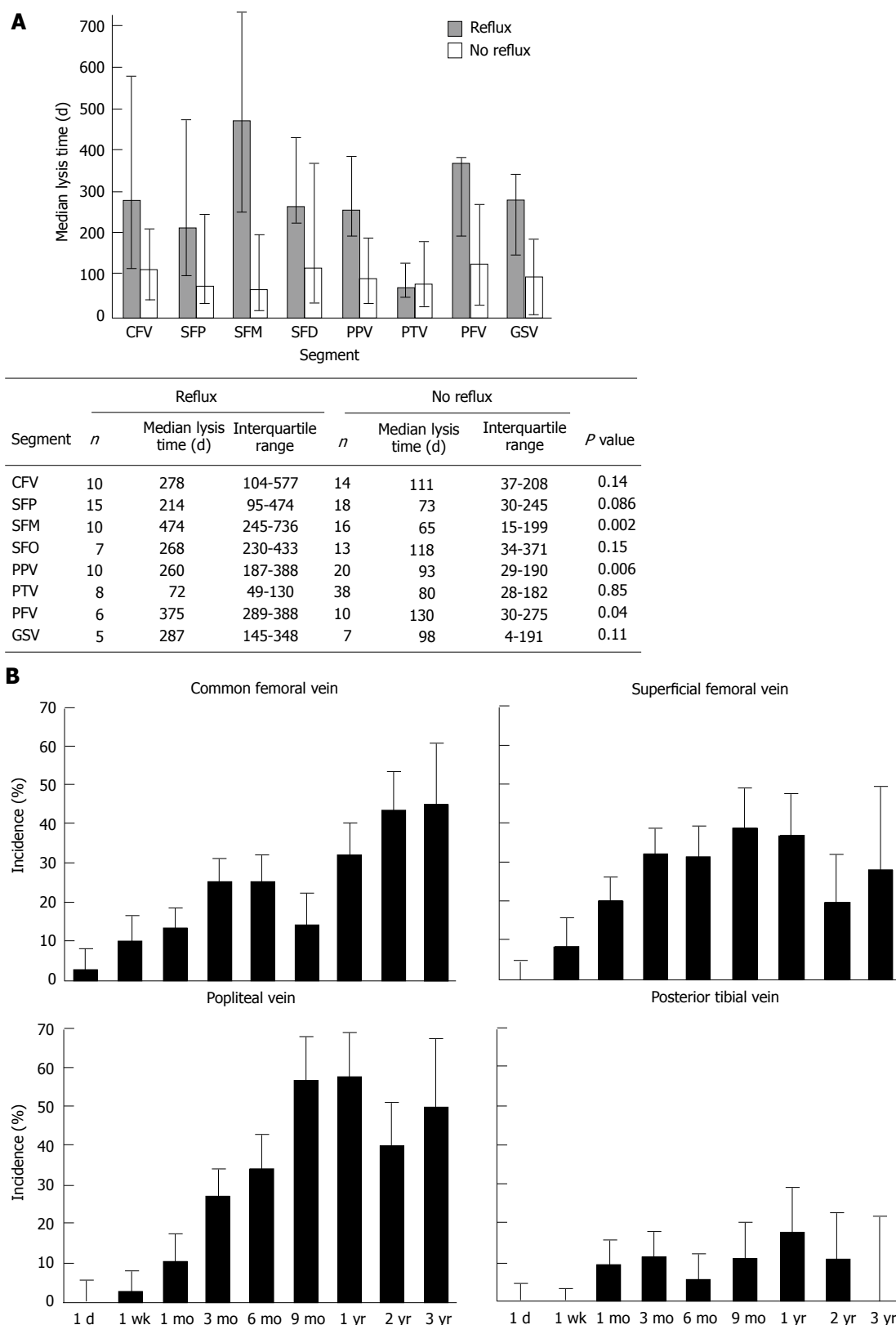


Figure 2 Recanalization of proximal deep vein thrombosis is usually delayed and may be completed after 3, 6 to 9 mo post-deep vein thrombosis with a high incidence of reflux, deep vein thrombosis recurrence and PTS. A: The relationship between the time of complete recanalization after deep vein thrombosis (DVT) (lysis time of leg vein thrombosis) appears to be 3 mo for those DVT patients who did not develop reflux, but appeared to be about 9 to 12 mo for those DVT patients who developed reflux as a main determinant for the development of PTS [Common femoral vein (CFV), superficial femoral vein (SFV), middle superficial femoral vein (SFM), distal superficial vein (SFD), popliteal vein (PPT), posterior tibial vein (PTV), greater saphena vein (GSV)]^[15]; B: Localization of reflux in patients with delayed recanalization (Figure 2A) of deep vein thrombosis^[15].

Of 58 VTE recurrent episodes, 41 occurred at time of RVT. The hazard ratio for recurrent VTE was 2.4 with

persistent RVT vs those with earlier complete vein recanalization^[19].

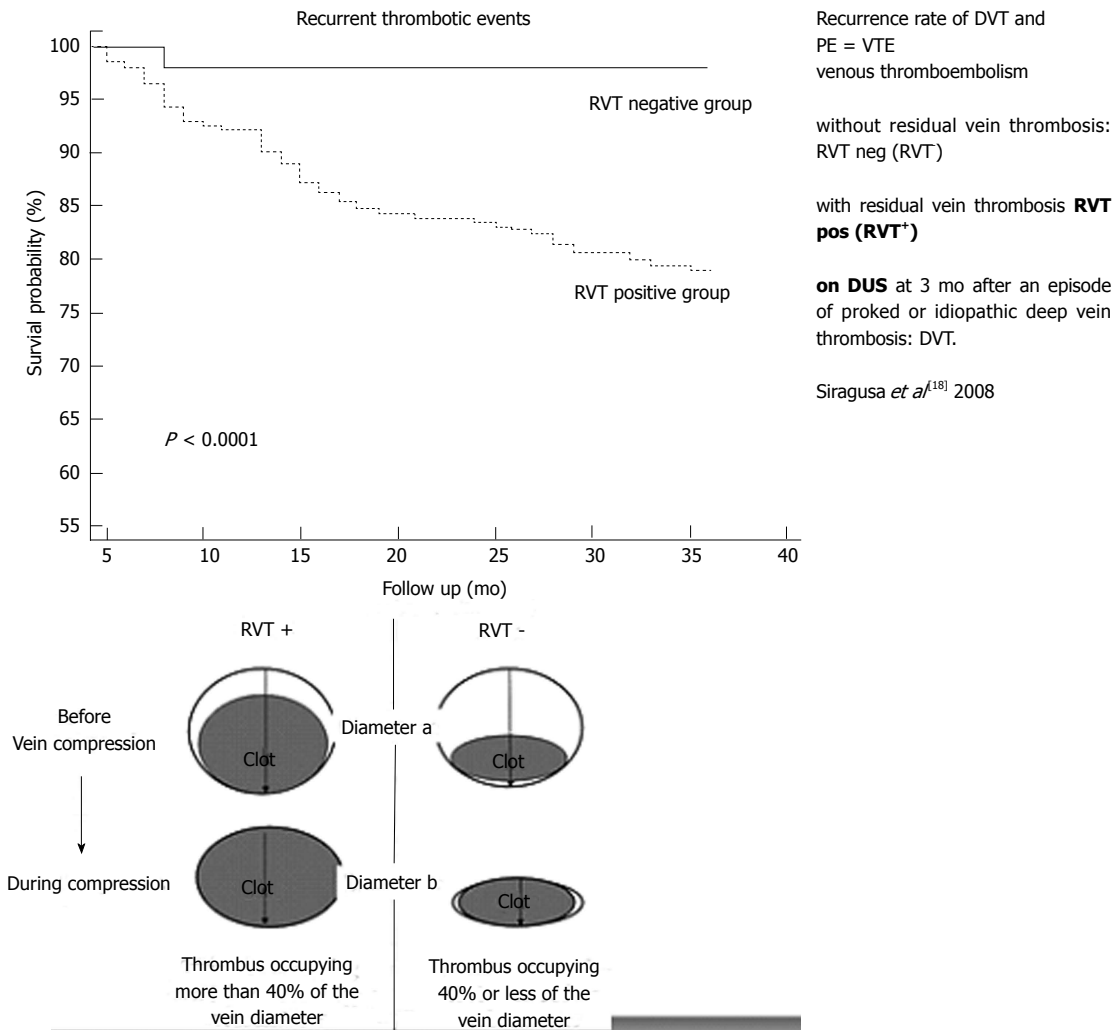


Figure 3 Event free recurrence rate of venous thromboembolism in 209 "low risk" DVT patients with no residual vein thrombosis at 3 mo post-DVT (RVT Neg in Table 3) as compared to 312 "high risk" DVT patients with RVT at 3 mo post-DVT (RVT Pos group in Table 3) after discontinuation of anticoagulation during 2 years follow-up in the prospective study of Siragusa *et al.*^[18] shown in Table 3. RVT: Residual vein thrombosis.

SCORING SYSTEMS FOR PTS

The fundamental pathophysiologic disturbance with severe leg symptoms or sign after distal and proximal DVT is sustained venous hypertension, which can be measured with invasive venous pressure measurement [ambulant venous pressure (AVP)]. AVP can be regarded as the gold standard, since it directly measures the pressure in the venous system of the lower extremity. This technique requires special equipment, is invasive, time consuming and cumbersome and therefore only suitable for basic research and scientific studies.

Identification of no, early and late PTS in patients after a first or recurrent DVT is not reflected by the clinical, etiological, anatomical and pathological (CEAP) classification and remains a challenge for clinicians and phlebologists. Several means of measuring and classifying the early clinical signs and symptoms of PTS and its long-term sequelae of PTS

Table 2 Scoring system according to Prandoni for the assessment of post-thrombotic syndrome in the early period 3 to 12 mo post-DVT known as the Vilalta score^[29-31]

Subjective symptoms	Objective signs
Heaviness	Pretibial oedema
Pain	Induration of the skin
Cramps	Hyperpigmentation
Pruritus	New venous ectasia
Paraesthesia	Redness
Pain during calf compression	
Ulceration of the skin (= severe)	
Each sign or symptom is graded with a score as 0, 1, 2, or 3	
0 = absent, 1 = mild, 2 = moderate or interference with daily life and work, 3 = severe or invalidating	
The presence or absence of leg ulcer has to be noted	
Definition of post-thrombotic syndrome according to Prandoni(Vilalta)	
Absent	Score < 4
Mild-to-moderate	core between 5 and 14 at 2 consecutive visits
Severe	score > 15 at 2 consecutive occasions or ulcer at 1 occasion

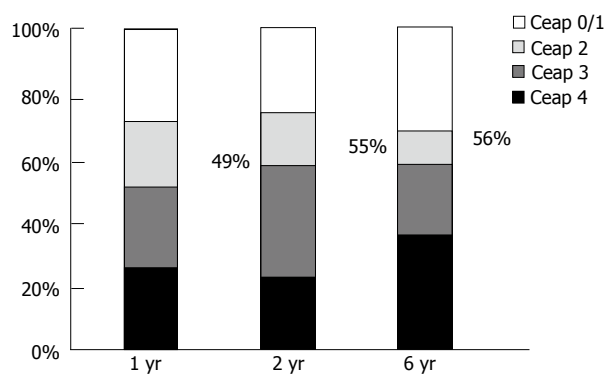


Figure 4 Incidence of the post-thrombotic syndrome according to the CEAP classification in patients with deep vein thrombosis during long-term follow-up^[32].

Table 3 Clinical-etiology-anatomic-pathophysiologic classification for severity of chronic venous insufficiency^[26]

Classification	Symptom
C0 (C = Clinical)	No visible varicose veins
C1	Spider or reticular veins
C2	Varicose veins
C3	Oedema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Skin changes with healed ulceration
C6	Skin changes with active ulceration
S	Symptomatic, including aches, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
C = Clinical symptom	Post-DVT
E = Etiology	Deep, perforator, or superficial vein, alone or in combination
A = Anatomic distribution	Reflux or obstruction, alone or in combination
P = Pathophysiologic dysfunction	

Table 4 Widmer classification for assessment of chronic venous insufficiency^[27]

Classification	Symptom
I	Corona phlebomatosa paraplantaris (ankle flare), subclinical mild oedema
II	Hyperpigmentation, lipo- and dermatosclerosis, atrophie blanche (white skin atrophy), oedema, eczema
III	Healed or active ulcer

exist. Most scoring systems for PTS are based on the presence or absence clinical signs and symptoms during the first year post-DVT and typical signs of CVI one or few years later. At least five definitions for early and/or late PTS exist for the early or long-term complications after an episode of documented DVT. For the prevention and management of PTS, it is crucial that the natural history and treatment outcome of the disease should be documented

Table 5 Venous clinical severity score system of PTS or chronic venous insufficiency^[28]

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
Varicose veins	None	Few, scattered: branch varicose veins	Multiple: GS varicose veins confined to calf or thigh	Extensive: thigh and calf or GS and LS distribution
Venous oedema	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
Skin pigmentation	Non or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Entire lower third of leg or more
No. of active ulcers	0	1	> 2	> 2
Active ulceration, duration	None	< 3 mo	> 3 mo, < 1 yr	Not healed > 1 yr
Active ulcer, size	None	< 2 cm diameter	2 to 6 cm diameter	> 6 cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings + elevation

GS: Greater saphenous; LS: Lesser saphenous.

by additional objective tools including residual vein thrombosis (RVT) on DUS, and reflux and/or obstruction on color ultrasonography (Table 1)^[20-25]. At the baseline visit the clinicians should carefully examine the patient's leg to classify the clinical category and to assess the severity of early PTS or late CVI using the different scoring systems. The five scoring systems including the clinical classifications by Brandjes *et al.*^[24] and by Prandoni *et al.*^[25] (known as the Villalta score^[25-28]) for early signs and symptoms of PTS during the first year post-DVT, and the CEAP, Widmer and VCS classifications to assess various degrees CVI as late onset sequelae of PTS are presented in Tables 1-5^[29-31].

Two classifications for early PTS have been used

Table 6 2008 Rotterdam objective scoring system for grading the severity of PTS during the first two years post-DVT based on prospective studies^[20-25]: therapeutic implications

Objective score	
Complete recanalization at 3 mo and no reflux	0
Incomplete recanalization at 3 mo	2
Complete recanalization after 6 mo and reflux	1
Incomplete recanalization after 6 mo and reflux	2
Obstruction after 1 year without or with reflux	3
Normal D-dimer after discontinuation of anticoagulant therapy	0
Increased D-dimer after discontinuation of anticoagulant therapy	3
Clinical score	
Brandjes Prandoni score for PTS: Absent	0
Mild	1
Moderate	2
Total Rotterdam score 12	
Score	Therapeutic implication
Score 0 at 6 mo	No MECS and no ACT
Score 1 to 4 at 6 mo	MECS and discontinuation ACT
Score > 4 and normal D-dimer	MECS randomization ACT vs no ACT
Score > 4 and abnormal D-dimer	MECS and continuation of ACT according to the PROLONG Plus Study
Designed by Michiels	

ACT: Anticoagulant treatment.

by clinicians. The first clinical scoring system of Brandjes was developed in 1991 for early PTS during the first two years after DVT to assess the effect of wearing stockings. It had an equivalent system of subjective signs and objective symptoms, and both are graded as absent or present (Table 1)^[24]. The Brandjes scoring system mild-to-moderate PTS as score 3 or more including one objective criterion. Severe PTS is assessed separately and consists of a score of 4 or more (Table 1). As the extension of the Brandjes scoring system, Prandoni developed a simplified clinical scoring system for PTS in a series of patients with overt PTS and patients without any sign and symptoms of PTS (Table 2), and validated his scoring system in prospective studies^[29-31].

Three classifications for PTS have been used by dermatologists and phlebologist the CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) (Table 3)^[26] Widmer *et al.*^[27] (Table 4) and the venous clinical severity (VCS) score (Table 5)^[28]. Clinical symptoms of PTS occurs in about half of the patients within one year post-DVT. A Dutch study prospectively evaluated the incidence and severity of PTS in 93 DVT patients under careful clinical survey using the CEAP classification and confirmed previous studies that half of DVT patients do develop PTS (Figure 4)^[32]. The cumulative incidence of PTS increased from 49%

after one year to 55% and 56% after 2 and 6 years, but class 5 and 6 (healed) ulcers did not occur while on treatment with MECS (Figure 4).

PREVENTION OF DVT RECURRENCE AND PTS

The incidence of DVT recurrence in the PROLONG and other studies in post-DVT patients with normal vs increased D-dimer levels one month after anticoagulation discontinuation was about 5% pt-years and 10%-5% pt/years respectively^[20-22]. This difference was independent from other factors like thrombophilia or residual venous occlusion. In the PROLONG study, extended anticoagulation reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer^[23]. These data has to be interpreted in view of two other key observations: first the incidence of DVT recurrence after complete recanalization within 3 mo and no reflux is very low^[15,16,18]. Second the incidence of PTS in the control arm of two randomized clinical trials was about 50% within 6 mo and did not significantly increase thereafter, whereas MECS decreased the incidence of PTS from around 50%-25% after two years follow-up^[24,25]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer do occur in those with incomplete or complete RVT after 6 mo with reflux (Table 1). The hypothesis in Table 6 that the Rotterdam scoring system for PTS will have therapeutic implications has to be tested by the use of objective measurements of RVT and reflux related to clinical score for PTS in prospective management and outcome studies.

Patients provoked and unprovoked DVT at time of diagnosis should be included in prospective studies on bridging the gap between DVT and PTS. All acute DVT patients are instructed to use medical elastic stockings for at least 3 to 6 mo (Figures 6 and 7). All DVT patients should be followed up by the combine use of the Prandoni (Vilalta) score and CEAP assessment for PTS at 1, 3, 6, 9 and 12 mo post-DVT. Patients with acute DVT should be followed up by CUS for the degree of recanalization and PTS symptoms at 1, 3, and 6 mo post-DVT. About one third to half of the DVT patients do not develop PTS at 3 to 6 mo post-DVT and do not need to wear medical elastic compression stockings (Study arm 1 Figures 6 and 7)^[33]. Rapid and complete recanalization of DVT with no residual vein thrombosis (RVT) at 3 mo post-dVT is followed by a very low risk of DVT recurrence after anticoagulant discontinuation (study arm 1, Figures 6 and 7), whereas a delayed recanalization of DVT with RVT at 3 mo post-DVT is associated with a high risk on DVT recurrence and PTS (Study arm 2, Figures 6

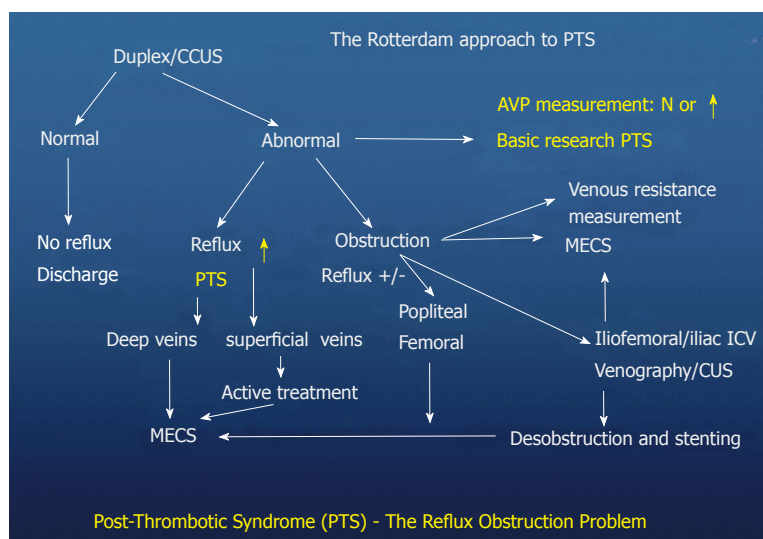


Figure 5 Rotterdam approach to the post-thrombotic syndrome according to Wentel *et al*^[33]. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

Erasmus study: DVT and PTS vs MECS or not

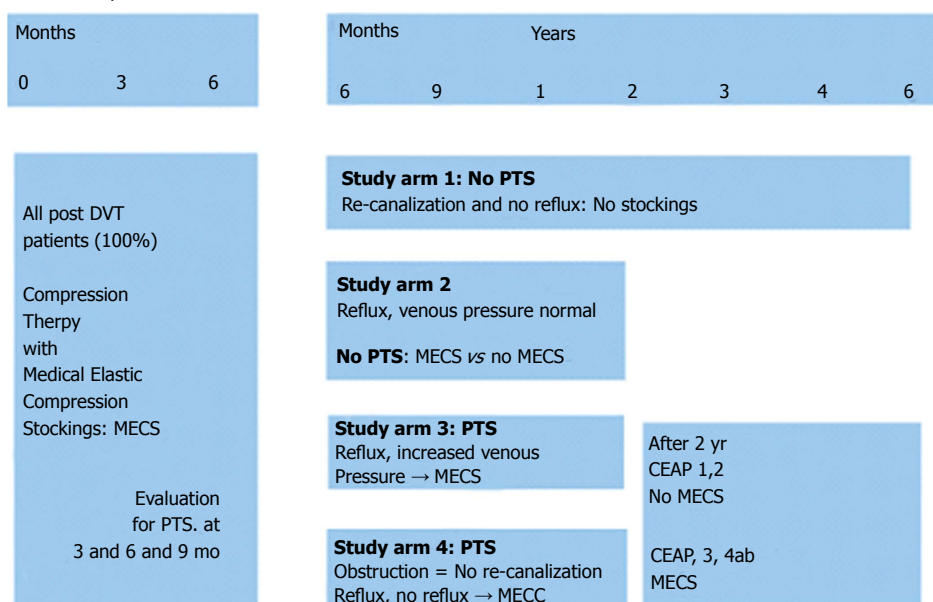


Figure 6 2007 Rotterdam Erasmus study design, time schedule, clinical score assessment and procedures for prospective evaluation of post-DVT venous thromboembolism-recurrence and postthrombotic syndrome. PTS: Postthrombotic syndrome; MECS: Medical elastic compression stockings.

and 7). If no pathological changes on DUS with complete recanalization, no reflux and no PTS at 3 to 9 mo post-DVT it is predicted that DVT recurrence rate and PTS remain low after anticoagulation discontinuation. Patients with PTS according to the prandoni (Villalta) score and/or CEAP assessment at 6, 9 and 12 mo post-DVT are candidates for continuation to wear MECS and the need to prolong anticoagulation for at least 24 mo to several years (Study arms 3 and 4, Figures 6 and 7).

ERASMUS STUDY DESIGNS TO PREVENT DVT RECURRENCE AND PTS WITH MECS

Study arm 1

Post-DVT patients with complete re-canalisation at 3 mo, no reflux, and asymptomatic (no PTS) will dis-

continue MECS and anticoagulant treatment (Figure 6).

Study arm 2

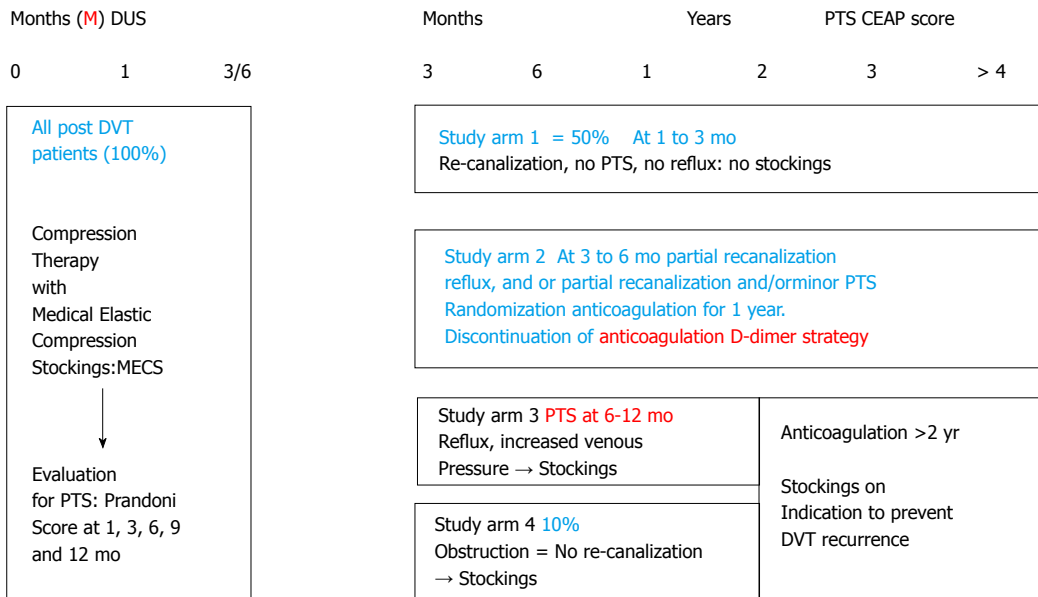
Post-DVT patients with reflux and no PTS will be randomized for MECS vs no MECS to address the question whether MECS is needed.

Study arm 3

MECS is recommended in symptomatic (PTS patients with delayed recanalization, reflux and increased ambulatory venous pressure for 2 years followed by randomization between continuation vs discontinuation of MECS for another 2 years.

Study arm 4

PTS patients with obstruction are candidates for MECS for 2 years followed by randomization between



The Rotterdam Erasmus PTS study design 2014 Michiels, Strijkers, and Wittens

Figure 7 European DVT - postthrombotic syndrome Bridging the Gap study design 2014. MECS: Medical elastic compression stockings.

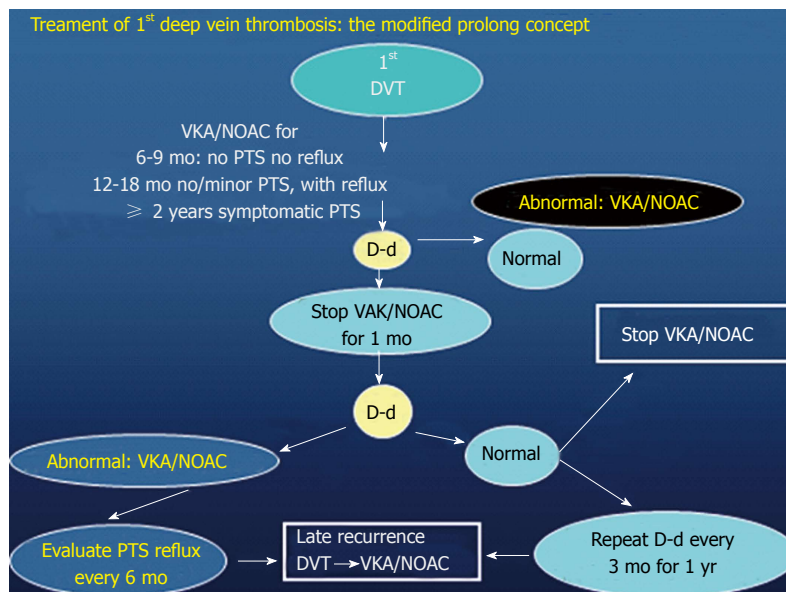


Figure 8 Algorithm modification of the D-dimer strategy according to the modified PROLONG study 23 for the duration and extension of anticoagulant treatment in post-DVT patients on top of objective risk stratification in Figure 7.

continuation and discontinuation of MECS for at least another 2 years.

PTS patients in study arm 3 and 4 are in need for extended anticoagulation according to the PROLONG study (Figures 7 and 8).

Evaluation procedures

At time of inclusion 1 mo and 3 mo after DVT:

Evaluation of clinical findings and details of positive echogram for DVT from the records of various hospitals or medical diagnostic centers where the diagnosis of DVT was made. Blood collection (plasma, serum and DNA samples in deep freezer) for risk factor evaluation in retrospect.

Evaluation at time points 1 mo, 3 mo and 6

mo, 1 year, and 2 years post-DVT: (1) complete analysis for PTS according to subjective Prandoni (Vilalta) score and according to objective CEAP score; (2) DUS colour at 3 and 6 mo for assessment of the degree of recanalization, reflux and obstruction; (3) allocation of PTS patients at 6 mo to each of the four study arms; (4) randomization of study arm 2 at time point 6 mo into no MECS versus MECS; (5) at time point 2 years randomization of PTS patients arm 3 and 4 into MECS versus no MECS; and (6) repeat all measurements for PTS according to subjective Prandoni (Vilalta) score, and CEAP classification, and assess the degree of recanalization, reflux and obstruction by DUS and colour Doppler at 9, 12, 18 and 24 mo during follow-up.

Real life documentation of DVT patients and the need of extended anticoagulation: All patients with provoked and unprovoked DVT will be treated immediately with Direct Oral Anticoagulants (DOACs) for 6 mo (Figures 6 and 7) and will undergo a complete evaluation for PTS at 3 and 6 mo post-DVT. Four groups of PTS at 6 mo post-DVT are distinguished depending on objective measurement criteria for PTS (Table 2) and allocated to the four study arms of the study design (Figures 6 and 7). Group 1: rapid and complete recanalization within 3 mo, no reflux at 6 mo post-DVT, and no PTS for which anticoagulation and MECS can be discontinued at 6 mo post-DVT. Group 2, no PTS with reflux of the deep venous system and no PTS when wearing MECS for which anticoagulation should be continued until re-evaluation at 1 year post DVT. Group 3 and 4 PTS with reflux and incomplete recanalization or obstruction at 6-12 mo post-DVT are candidates for long-term anticoagulation and MECS for at least 2 years or even longer to prevent DVT recurrence to prevent progression of PTS. A large scale prospective study is warranted to fine-tune and prove this concept.

Palareti *et al*^[20] and other studies showed that normal versus increased D-dimer levels one month after anticoagulation discontinuation is related to a low versus high DVT recurrence rate of 5% patient-years vs 10%-15% patient-years respectively^[20-23]. Such post-DVT patients with increased sensitive D-dimer after discontinuation surely belong to the group of symptomatic post-DVT patients at high risk to develop PTS (score ≥ 3 , Table 1 integrated in the algorithm in Figures 7 and 8)^[23,35]. In the prolong study, extended anticoagulation in post-DVT patients with increased D-dimer above the upper limit of normal will reduced the risk of DVT recurrence from 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased, 4.4% patient/years, in post-DVT patients with a normal D-dimer on month after discontinuation of regular anticoagulation^[23,34]. This may implicate that DVT recurrence in those patients with either a normal or increased D-dimer very likely do occur in those with incomplete or complete recanalization of the leg veins after 6 mo with reflux score 3 or more (Table 6). This important observation has been confirmed by Latella *et al*^[35] in a prospective study of 305 DVT patients selected for quantitative ELISA D-dimer (VIDAS) measurement 4 mo post-DVT. Of these 305 (46%) developed PTS (mild 25%, moderate 13%, severe 7%) and 54% did not during 24 mo follow-up. Mean D-dimer level measured 4 mo post-DVT were significantly higher in patients with PTS vs without PTS (712 vs 444 $\mu\text{g/L}$ $P = 0.02$)^[35]. At time of D-dimer measurement 213 were taken anticoagulants. The PROLONG study^[23] demonstrated the need to continue anticoagulant treatment in post-DVT patients with increased

D-dimer level during anticoagulant treatment and when D-dimer levels are above the upper level of normal one month after discontinuation of anticoagulant treatment (Figures 7 and 8)^[34,35].

ACKNOWLEDGMENTS

The present report on DVT and PTS Bridging the Gap study was designed and written between 2007 and 2013 by Dr. Michiels in his position of Senior Investigator, Phlebology at the Department of Dermatology, Erasmus University Medical Center Rotterdam (Chief professor H.A. Martino Neumann).

REFERENCES

- 1 **Freyburger G**, Trillaud H, Labrousse S, Gauthier P, Javorschi S, Bernard P, Grenier N. D-dimer strategy in thrombosis exclusion--a gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. *Thromb Haemost* 1998; **79**: 32-37 [PMID: 9459318]
- 2 **van der Graaf F**, van den Borne H, van der Kolk M, de Wild PJ, Janssen GW, van Uum SH. Exclusion of deep venous thrombosis with D-dimer testing--comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thromb Haemost* 2000; **83**: 191-198 [PMID: 10739371]
- 3 **Perrier A**, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, Didier D, Unger PF, Patenaud JV, Bounameax H. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; **353**: 190-195 [DOI: 10.1016/S0140-6736(98)05248-9]
- 4 **Oudega R**, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost* 2005; **94**: 200-205 [PMID: 16113804]
- 5 **Oudega R**, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. *Ann Intern Med* 2005; **143**: 100-107 [PMID: 16027451 DOI: 10.7326/0003-4819-143-2-200507190-00008]
- 6 **Schutgens RE**, Ackermans P, Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pijlman AH, Pruijm M, Oltmans R, Kelder JC, Biesma DH. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation* 2003; **107**: 593-597 [PMID: 12566372 DOI: 10.1161/01.CIR.0000045670.12988.1E]
- 7 **Wells PS**, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, Massicotte MP, Hirsh J, Weitz JJ, Kearon C. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 1995; **91**: 2184-2187 [PMID: 7697847 DOI: 10.1161/01.CIR.91.8.2184]
- 8 **Michiels JJ**, Gadisseur A, Van Der Planken M, Schroyens W, De Maeseneer M, Hermens JT, Trienekens PH, Hoogsteden H, Pattynama PM. A critical appraisal of non-invasive diagnosis and exclusion of deep vein thrombosis and pulmonary embolism in outpatients with suspected deep vein thrombosis or pulmonary embolism: how many tests do we need? *Int Angiol* 2005; **24**: 27-39 [PMID: 15876996]
- 9 **Michiels JJ**, Gadisseur A, van der Planken M, Schroyens W, De Maeseneer M, Hermens JT, Trienekens PH, Hoogsteden H, Pattynama PM. Different accuracies of rapid enzyme-linked immunosorbent, turbidimetric, and agglutination D-dimer assays for thrombosis exclusion: impact on diagnostic work-ups of outpatients with suspected deep vein thrombosis and pulmonary embolism. *Semin Thromb Hemost* 2006; **32**: 678-693 [PMID: 17024595 DOI: 10.1055/s-2006-951296]
- 10 **Oudega R**, Toll DB, Bulten RJ, Hoes AW, Moons KG. Different

- cut-off values for two D-dimer assays to exclude deep venous thrombosis in primary care. *Thromb Haemost* 2006; **95**: 744-746 [PMID: 16601850]
- 11 **Kraaijenhagen RA**, Piovella F, Bernardi E, Verlato F, Beckers EA, Koopman MM, Barone M, Camporese G, Potter Van Loon BJ, Prins MH, Prandoni P, Büller HR. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med* 2002; **162**: 907-911 [PMID: 11966342 DOI: 10.1001/archinte.162.8.907]
- 12 **Tick LW**, Ton E, Voorthuizen TH, Hovens MMC, Leeuwenburgh I, Lobatto S, Stijnen PJ, van der Heul C, Huisman PM, Kramer MHH, Huisman MV. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography and D-dimer test. *Am J Med* 2002; **113**: 630-635 [DOI: 10.1016/S0002-9343(02)01347-5]
- 13 **Wells PS**, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; **349**: 1227-1235 [PMID: 14507948 DOI: 10.1056/NEJMoa023153]
- 14 **Kearon C**, Ginsberg JS, Douketis J, Crowther MA, Turpie AG, Bates SM, Lee A, Brill-Edwards P, Finch T, Gent M. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. *Ann Intern Med* 2005; **142**: 490-496 [PMID: 15809460 DOI: 10.7326/0003-4819-142-7-200504050-00007]
- 15 **Meissner MH**, Manzo RA, Bergelin RO, Markel A, Strandness DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg* 1993; **18**: 596-605; discussion 606-608 [PMID: 8411467 DOI: 10.1016/0741-5214(93)90069-X]
- 16 **Markel A**, Manzo RA, Bergelin RO, Strandness DE. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. *J Vasc Surg* 1992; **15**: 377-382; discussion 383-384 [PMID: 1735898 DOI: 10.1016/0741-5214(92)90259-B]
- 17 **Markel A**. Origin and natural history of deep vein thrombosis of the legs. *Semin Vasc Med* 2005; **5**: 65-74 [PMID: 15968582 DOI: 10.1055/s-2005-871743]
- 18 **Siragusa S**, Malato A, Anastasio R, Cigna V, Milio G, Amato C, Bellisi M, Attanzio MT, Cormaci O, Pellegrino M, Dolce A, Casuccio A, Bajardi G, Mariani G. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood* 2008; **112**: 511-515 [PMID: 18497320 DOI: 10.1182/blood-2008-01-131656]
- 19 **Prandoni P**, Lensing AW, Prins MH, Bernardi E, Marchiori A, Bagatella P, Frulla M, Mosena L, Tormene D, Piccioli A, Simioni P, Girolami A. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med* 2002; **137**: 955-960 [PMID: 12484710 DOI: 10.7326/0003-4819-137-12-200212170-00008]
- 20 **Palareti G**, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thromb Haemost* 2002; **87**: 7-12 [PMID: 11848459]
- 21 **Palareti G**, Legnani C, Cosmi B, Valdré L, Lunghi B, Bernardi F, Coccheri S. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003; **108**: 313-318 [PMID: 12847064 DOI: 10.1161/01.CIR.0000079162.69615.0F]
- 22 **Eichinger S**, Minar E, Bialonczyk C, Hirschl M, Quehenberger P, Schneider B, Weltermann A, Wagner O, Kyrle PA. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA* 2003; **290**: 1071-1074 [PMID: 12941680 DOI: 10.1001/jama.290.8.1071]
- 23 **Palareti G**, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; **355**: 1780-1789 [PMID: 17065639 DOI: 10.1056/NEJMoa054444]
- 24 **Brandjes DP**, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; **349**: 759-762 [PMID: 9074574 DOI: 10.1016/S0140-6736(96)12215-7]
- 25 **Prandoni P**, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, Tormene D, Mosena L, Pagnan A, Girolami A. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004; **141**: 249-256 [PMID: 15313740 DOI: 10.7326/0003-4819-141-4-200408170-00004]
- 26 **Eklöf B**, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC, Wakefield TW. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004; **40**: 1248-1252 [PMID: 15622385 DOI: 10.1016/j.jvs.2004.09.027]
- 27 **Widmer LK**, Plechl SC, Leu HJ, Boner H. [Venous diseases in 1800 employees. Basel Studies II]. *Schweiz Med Wochenschr* 1967; **97**: 107-110 [PMID: 6032299]
- 28 **Rutherford RB**, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: An adjunct to venous outcome assessment. *J Vasc Surg* 2000; **31**: 1307-1312 [PMID: 10842165 DOI: 10.1067/mva.2000.107094]
- 29 **Prandoni P**, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**: 1-7 [PMID: 8644983 DOI: 10.7326/0003-4819-125-1-199607010-00001]
- 30 **Bernardi E**, Bagatella P, Frulla M, Simioni P, Prandoni P. Postthrombotic syndrome: incidence, prevention, and management. *Semin Vasc Med* 2001; **1**: 71-80 [PMID: 15199516 DOI: 10.1055/s-2001-14543]
- 31 **Pesavento R**, Bernardi E, Concolato A, Dalla Valle F, Pagnan A, Prandoni P. Postthrombotic syndrome. *Semin Thromb Hemost* 2006; **32**: 744-751 [PMID: 17024603 DOI: 10.1055/s-2006-951460]
- 32 **Roumen-Klappe EM**, den Heijer M, Janssen MC, van der Vleuten C, Thien T, Wollersheim H. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. *Thromb Haemost* 2005; **94**: 825-830 [PMID: 16270638]
- 33 **Wentel TD**, Neumann HA. Management of the postthrombotic syndrome: the Rotterdam approach. *Semin Thromb Hemost* 2006; **32**: 814-821 [PMID: 17171595 DOI: 10.1055/s-2006-955469]
- 34 **Michiels JJ**, Moosdorff W, Maasland H, Michiels JM, Lao MU, Neumann HA, Dulicek P, Stvrtinova V, Barth J, Palareti G. Duplex ultrasound, clinical score, thrombotic risk, and D-dimer testing for evidence based diagnosis and management of deep vein thrombosis and alternative diagnoses in the primary care setting and outpatient ward. *Int Angiol* 2014; **33**: 1-19 [PMID: 24452081]
- 35 **Latella J**, Desmarais S, Miron MJ, Roussin A, Joyal F, Kassir J, Solymoss S, Desjardins L, Ginsberg JS, Kahn SR. Relation between D-dimer level, venous valvular reflux and the development of post-thrombotic syndrome after deep vein thrombosis. *J Thromb Haemost* 2010; **8**: 2169-2175 [PMID: 20670369 DOI: 10.1111/j.1538-7836.2010.04001.x]

P- Reviewer: Hassan M S- Editor: Qi Y
L- Editor: A E- Editor: Wu HL



Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy

Hiroshi Yasuda, Yasumasa Matsuo, Yoshinori Sato, Sun-ichiro Ozawa, Shinya Ishigooka, Masaki Yamashita, Hiroyuki Yamamoto, Fumio Itoh

Hiroshi Yasuda, Yasumasa Matsuo, Yoshinori Sato, Sun-ichiro Ozawa, Shinya Ishigooka, Masaki Yamashita, Hiroyuki Yamamoto, Fumio Itoh, Division of Gastroenterology and Hepatology, St. Marianna University School of Medicine, Kawasaki 216-8511, Japan

Author contributions: All authors contributed to this work.

Conflict-of-interest: There are no conflicts of interest to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Hiroshi Yasuda, MD, PhD, Division of Gastroenterology and Hepatology, St. Marianna University School of Medicine, 2-16-1 Sugao, Kawasaki 216-8511, Japan. hyasuda@marianna-u.ac.jp

Telephone: +81-44-9778111

Fax: +81-44-9765805

Received: September 26, 2014

Peer-review started: September 28, 2014

First decision: December 17, 2014

Revised: December 26, 2014

Accepted: January 15, 2015

Article in press: January 15, 2015

Published online: February 4, 2015

antiplatelet therapy with proton-pump inhibitors (PPIs) is recommended to prevent further ischemic events. PPI prophylaxis during antiplatelet therapy reduces the risk of upper gastrointestinal bleeding. The potential negative metabolic interaction between PPIs and clopidogrel is still unclear.

Key words: Antiplatelet therapy; Aspirin; Clopidogrel; Gastrointestinal bleeding; Endoscopy; Proton-pump inhibitor

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Gastrointestinal bleeding (GIB) is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening. Prophylaxis with antisecretory drugs such as proton-pump inhibitors reduces the risk of GIB.

Yasuda H, Matsuo Y, Sato Y, Ozawa S, Ishigooka S, Yamashita M, Yamamoto H, Itoh F. Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy. *World J Crit Care Med* 2015; 4(1): 40-46 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/40.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.40>

Abstract

Antiplatelet therapy is the standard of care for the secondary prevention of acute coronary syndrome and ischemic stroke, especially after coronary intervention. However, this therapy is associated with bleeding complications such as gastrointestinal bleeding, which is one of the most common life-threatening complications. Early endoscopy is recommended for most patients with acute upper gastrointestinal bleeding. After successful endoscopic hemostasis, immediate resumption of

INTRODUCTION

Antiplatelet therapy is widely used in the secondary prevention of acute coronary syndrome (ACS) and ischemic stroke, especially after interventional

therapy. Dual antiplatelet therapy (DAPT) with aspirin plus a thienopyridine derivative that inhibits the platelet P2Y₁₂ adenosine diphosphate (ADP) receptor is the standard treatment to prevent stent thrombosis after implantation of drug-eluting stents (DESs) in patients with symptomatic coronary artery disease^[1,2]. The joint guidelines of the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions recommend that aspirin therapy should be continued lifelong in all patients with ST-elevation myocardial infarction (MI)-ACS, and clopidogrel or prasugrel should be administered for at least 12 mo in patients receiving stents (bare metal stents or DESs) during percutaneous coronary intervention (PCI) for ACS^[3,4]. Antiplatelet therapy is also used for both the management and the prevention of acute ischemic stroke. Aspirin is the most commonly used agent in this therapy. Long-term administration of clopidogrel in patients with ischemic stroke is also beneficial and induces a slightly lower frequency of gastrointestinal bleeding (GIB) than does aspirin administration^[5].

Antiplatelet therapy is associated with bleeding complications such as GIB, which is one of the most common life-threatening complications of this therapy^[6-9]. This review focuses on the management and prevention of upper GIB in patients receiving antiplatelet therapy.

ANTIPLATELET THERAPY AND GIB

Antiplatelet therapy causes GIB, especially in elderly patients. Usually, clinically important upper GIB is identified by hematemesis and/or melena and a decrease in hemoglobin level of at least 2 g/dL, and is confirmed by an endoscopic diagnosis of peptic ulcer lesions as the cause of bleeding. Antiplatelet therapy-related ulcers often occur without symptoms of dyspepsia. Aspirin and P2Y₁₂ inhibitors are the most common antiplatelet agents. Aspirin irreversibly inhibits cyclooxygenase-1 by acetylating a serine residue at position 530, thereby preventing the conversion of arachidonate to the prostaglandin PGH₂, which is converted to the platelet agonist thromboxane^[10]. Several randomized trials (RCTs) have documented that patients with prior cardiovascular disease experience fewer cardiovascular events and deaths with the use of low-dose aspirin (LDA) therapy than without its use^[11,12]. LDA is commonly defined as aspirin between 75 and 325 mg/d. A meta-analysis indicated that no additional benefit was observed with the use of a higher dose of aspirin (300 mg/d vs 50-100 mg/d^[12]). LDA is an effective therapy for the secondary prevention of cardiovascular events and ischemic stroke.

Thienopyridines affect the ADP pathway by irreversibly blocking the ADP receptor P2Y₁₂, thereby inhibiting the activation of the glycoprotein II b/III

a complex and platelet aggregation^[10,13]. Ticlopidine, clopidogrel, and prasugrel are thienopyridine prodrugs that require conversion to an active metabolite. Ticagrelor belongs to a new family of antiplatelet agents, which directly and reversibly bind to the P2Y₁₂ receptor. The antiplatelet effects of the P2Y₁₂ inhibitor are additive to those of aspirin. The benefits of DAPT over aspirin alone in patients with ACS without ST-segment elevation were established in the Clopidogrel in Unstable Angina to Prevent Recurrent Events CURE trial^[14]. Analysis of a subset of patients in the CURE trial also showed the efficacy of DAPT in PCI^[15].

Incidence and risk factors of GIB

The reported risk factors for upper GIB include increasing age, female sex, major organ dysfunction (cardiac, respiratory, or hepatic), diabetes, hypertension, positive results for *Helicobacter pylori* infection, and hemostatic disorders^[7,16,17]. A case-control study showed that the odds ratios (ORs) for upper GIB in patients receiving LDA were similar to those in patients regularly receiving nonsteroidal anti-inflammatory drugs^[18]. A meta-analysis showed that there was an increased risk of major GIB with LDA use (OR = 1.55; 95%CI: 1.27-1.90^[19]). The risk of upper GIB associated with the use of thienopyridine monotherapy is reported to be similar to^[17] or greater than that associated with the use of aspirin alone^[14]. The risk of major bleeding is reportedly increased in patients receiving DAPT compared with those receiving aspirin monotherapy^[20]. In a population-based observational cohort study of elderly patients who survived MI, the rate of GIB was 1.5% per year with aspirin alone and 4.6% per year with aspirin plus clopidogrel or ticlopidine^[21]. Several large RCTs^[14,22-25] reported that 0.6% (28-d follow-up) to 4.8% (12-mo follow-up) of patients treated with DAPT experienced major bleeding, as compared with 0.6% (28-d follow-up) to 3.8% (12-mo follow-up) of patients treated with aspirin alone. An observational study reported that the 1- and 2-year cumulative incidences of upper GIB in patients who received DAPT without the use of an antisecretory drug [proton-pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA)] were 4.5% and 9.2%, respectively^[9]. Of note, the first month after PCI is a high-risk period for upper GIB^[9,17,26]. Further, the risk of GIB with triple therapy with warfarin, aspirin, and clopidogrel was reported to be as high as 5.1%^[27].

Outcomes of GIB

Bleeding complications are associated with an increased risk of recurrent ischemic events and death^[26,28]. In particular, GIB complicating PCI is associated with early mortality. In the Acute Catheterization and Urgent Intervention Triage Strategy trial, a large multicenter trial in patients

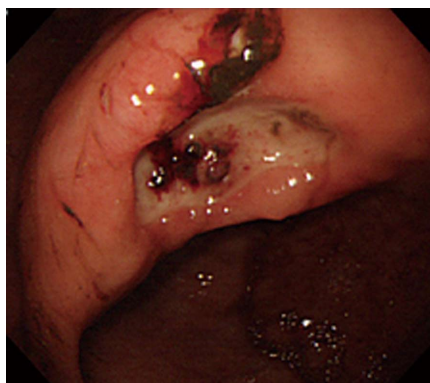


Figure 1 Peptic ulcer with an exposed vessel in a 68-year-old man 10 d after starting dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction.



Figure 2 Successful endoscopic hemostasis using endoclips.

with moderate- and high-risk ACS, GIB occurred in 1.3% of the patients and was found to be associated with longer hospital stays and higher 30-d all-cause mortality rates (9.6% vs 1.4% in patients with no bleeding^[29]). A retrospective study reported that the 30-d mortality rates were as high as 20.5% in patients with GIB, compared to 2.4% in those without GIB^[30]. The mechanism underlying the high rates of early mortality in ACS patients with GIB may be multifactorial. The risk of ischemic events is further aggravated by the augmented release of endogenous catecholamines and increased platelet adhesiveness in ACS patients with bleeding complications. Importantly, GIB is a well-known cause of premature cessation of antiplatelet therapy, which poses a serious risk of ischemic events during hospital stay and after hospital discharge.

MANAGEMENT OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Impact of blood transfusion on mortality after PCI

Major GIB often requires red blood cell (RBC) transfusions. Although RBC transfusions are performed to augment oxygen delivery to avoid the deleterious effects of oxygen debt, these transfusions may have potential harmful effects^[31]. Indeed, despite increased hemoglobin levels, RBC transfusion does not always increase tissue oxygenation. One possible explanation is that stored RBCs are low in 2,3-diphosphoglyceric acid; therefore, the hemoglobin will tend not to release oxygen to the tissues. In addition, RBCs mediate a nitric oxide-based hypoxic vasodilatory activity, which is impaired in banked blood, predisposing to vasoconstriction and ischemic insult^[32]. Therefore, blood transfusion does not always provide beneficial effects in ACS patients^[33]. A recent RCT in patients with acute upper GIB showed that a restrictive transfusion strategy (*i.e.*, transfusion when the hemoglobin level was < 7 g/dL) had significantly better outcomes than

a liberal transfusion strategy (*i.e.*, transfusion when the hemoglobin level was < 9 g/dL^[34]). Therefore, in patients with stable hemodynamic status, RBC transfusion is considered when the hemoglobin concentration falls below 7.0 g/dL in patients with stable angina and is 8-10 g/dL in those with ACS^[35].

Endoscopic hemostasis of GIB in patients receiving antiplatelet therapy

In patients with GIB, early endoscopy is beneficial for decreasing the length of hospital stay and avoiding surgical intervention^[36,37]. A case-control study reported that there were no serious complications of emergency endoscopy after MI^[17]. During endoscopy, careful removal of clots in an ulcer bed is important to detect the exposed vessel. When active spurting or oozing bleeding or a nonbleeding visible vessel is observed, endoscopic therapy should be provided to patients^[38]. Endoscopic hemostatic options include injection techniques using epinephrine or ethanol, ablative therapies such as use of a heater probe, coagulation with hemostatic forceps or argon plasma coagulation, and mechanical methods such as use of endoclips (Figures 1 and 2). Endoscopic treatment with a combination of epinephrine injection therapy and electrical coagulation or use of endoclips is also effective to achieve better outcomes. Routine second-look endoscopy is not recommended after successful endoscopic hemostasis with intravenous PPI therapy. Transcatheter arterial embolization can be considered for patients in whom endoscopic therapy has failed.

Continuation of antiplatelet therapy

GIB often causes premature cessation of antiplatelet therapy, which increases the thrombotic risk for cardiovascular and cerebrovascular events. A RCT in GIB patients receiving LDA therapy for the secondary prevention of cardiovascular disease showed that interruption of antiplatelet therapy is one of the most important determinants of fatal outcome. Although resumption of LDA therapy after endoscopic hemostasis was associated with a

50% increased risk of recurrent bleeding, the 8-wk mortality rate was significantly lower in the LDA group patients than in the placebo group patients (1.3% vs 12.9%^[39]). Thus, antiplatelet therapy and PPI cotherapy should be resumed immediately after the successful endoscopic control of ulcer bleeding to avoid further ischemic events.

PREVENTION OF GIB IN PATIENTS RECEIVING ANTIPLATELET THERAPY

Optimal duration and dosage of antiplatelet therapy

Risks of GIB increase with the use of multiple antiplatelet or anticoagulant agents and an increase in the duration of medication use. The optimal duration of antiplatelet therapy after PCI is unclear when thrombotic and bleeding risks are both taken into consideration. Although the current guidelines recommend that DAPT should be continued for at least 12 mo in patients receiving DESs during PCI for ACS, the long-term use of DAPT is associated with a higher rate of bleeding events^[40]. These guidelines are based on outcomes using first-generation DESs. Second-generation DESs, such as everolimus-eluting stents and zotarolimus-eluting stents, are now increasingly being used. Compared with first-generation DESs, second-generation DESs have equal or superior antirestenotic effects and lower stent thrombosis rates. Several studies have assessed the safety of a shorter duration of P2Y₁₂ inhibitor administration with second-generation DES use. A retrospective study reported that clopidogrel discontinuation before 1 year of therapy was associated with higher rates of stent thrombosis events for first-generation DESs but not for everolimus-eluting stents^[41]. The Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice trial showed that in patients undergoing PCI with zotarolimus-eluting stent implantation, short-term (3 mo) DAPT was noninferior to long-term (12 mo) DAPT for the occurrence of death, MI, and stroke, without significantly increasing the risk of stent thrombosis^[42]. Accordingly, DAPT duration could be potentially tailored to the type of stent used.

Prasugrel is a third-generation thienopyridine that provides more prompt, potent, and consistent platelet inhibition than does clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial demonstrated that prasugrel use (10 mg/d) resulted in significantly fewer ischemic events^[43]; however, a higher incidence of bleeding was observed with prasugrel use than with clopidogrel use in ACS patients undergoing PCI. Recently, the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study in Japanese ACS patients

undergoing PCI showed that a lower dose of prasugrel (3.75 mg/d) was associated with a low incidence of ischemic events, which is similar to the results of the TRITON-TIMI 38 trial, and with a low risk of clinically serious bleeding^[44]. In particular, interethnic differences should be taken into consideration in the management of patients receiving DAPT.

If PCI is required in patients taking oral anticoagulants, DAPT with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding^[27]. Omission of aspirin may be advantageous in such patients. Recently, the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing trial reported that the use of clopidogrel without aspirin was associated with a significant decrease in bleeding complications (2.9% vs 8.8%) without an increase in the rate of thrombotic events^[45]. Therefore, triple therapy may be discouraged in such patients with an indication for oral anticoagulants after PCI.

PPI prophylaxis

In patients receiving antiplatelet therapy, the concomitant use of an antisecretory agent is associated with a reduced risk of upper GIB. In particular, PPI use is associated with a substantial decrease in the risk of upper GIB in both LDA and clopidogrel users^[46]. Moreover, PPIs have been shown to be effective in preventing rebleeding after stabilization of upper GIB, which prevents the premature discontinuation of DAPT^[47]. In patients receiving LDA therapy for the secondary prevention of cardiovascular disease, use of H2RAs was associated with a risk of mucosal erosion but not of ulcer development^[48]. TAK-438, a novel potassium-competitive acid blocker, has also been shown to be as effective as PPIs in the prevention of aspirin-induced ulcer recurrence^[49]. A population-based study from Sweden reported that the risk of gastrointestinal ulcers depended on PPI adherence in patients receiving LDA therapy^[50]. After experiencing GIB, many patients stop receiving LDA therapy, which increases the risk of ischemic events. Therefore, physicians should encourage these patients to continue LDA therapy with PPI prophylaxis.

Potential metabolic interaction between PPIs and clopidogrel

Thienopyridine derivatives are prodrugs, which are metabolized into active forms through complex biochemical reactions involving several cytochrome P450 (CYP) isoforms including CYP2C19, which is also involved in the metabolism of PPIs. Several observational studies in clopidogrel recipients have shown a significant association between PPI use and cardiovascular events^[51,52]. A meta-analysis showed that there was an increased risk (OR =

1.43; 95%CI: 1.15-1.77) of adverse outcomes in patients co-prescribed clopidogrel and a PPI^[53]. Platelet studies have supported the use of PPIs with weaker inhibition of CYP2C19 (e.g., rabeprazole or pantoprazole^[54]). In contrast, in the Clopidogrel and the Optimization of Gastrointestinal Events trial of omeprazole vs placebo in coronary artery disease patients receiving aspirin and clopidogrel, no apparent cardiovascular interaction was observed between clopidogrel and omeprazole^[55]. Taken together, the potential negative interaction between PPI therapy and clopidogrel use is still controversial. Prasugrel is as effective as clopidogrel in the prevention of ischemic events^[43,44,56]. Of note, the platelet inhibitory activity of prasugrel is not affected by CYP2C19. Recently, the DOuble the dose of Clopidogrel or Switch to Prasugrel to Antagonize Proton pump inhibitor Interaction study reported that while the higher platelet inhibitory effect obtained by doubling the clopidogrel dose was completely neutralized by the coadministration of lansoprazole, this drug interaction was not observed with prasugrel^[57]. Furthermore, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes study, which compared prasugrel with clopidogrel in patients with unstable angina or MI without ST-segment elevation^[58], demonstrated that prasugrel was superior to clopidogrel in the subgroup of PPI users. The concomitant use of PPIs with prasugrel or ticagrelor may be beneficial for the prevention of upper GIB in patients receiving DAPT.

CONCLUSION

GIB is a relatively common complication in patients receiving antiplatelet therapy and is associated with an increased risk of recurrent ischemic events and mortality. Prophylaxis with antisecretory drugs such as PPIs reduces the risk of GIB. Early endoscopy is useful for both the diagnosis and the therapeutic management of GIB. Antiplatelet therapy should be resumed immediately after endoscopic hemostasis of GIB, unless the bleeding is life threatening.

REFERENCES

- 1 **Gurbel PA**, DiChiara J, Tantry US. Antiplatelet therapy after implantation of drug-eluting stents: duration, resistance, alternatives, and management of surgical patients. *Am J Cardiol* 2007; **100**: 18M-25M [PMID: 17950828]
- 2 **Brilakis ES**, Patel VG, Banerjee S. Medical management after coronary stent implantation: a review. *JAMA* 2013; **310**: 189-198 [PMID: 23839753 DOI: 10.1001/jama.2013.7086]
- 3 **Grines CL**, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Catheter Cardiovasc Interv* 2007; **69**: 334-340 [PMID: 17295287]
- 4 **Kushner FG**, Hand M, Smith SC, King SB, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009; **54**: 2205-2241 [PMID: 19942100 DOI: 10.1016/j.jacc.2009.10.015]
- 5 **CAPRIE Steering Committee**. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996; **348**: 1329-1339 [PMID: 8918275]
- 6 **Liberopoulos EN**, Elisaf MS, Tselepis AD, Archimandritis A, Kiskinis D, Cokkinos D, Mikhailidis DP. Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: where we are now? *Platelets* 2006; **17**: 1-6 [PMID: 16308180]
- 7 **Eikelboom JW**, Hirsh J. Bleeding and management of bleeding. *European Heart J* 2006; **Suppl 8**: G38-G45 [DOI: 10.1093/eurheartj/sul054]
- 8 **Shiotani A**, Kamada T, Haruma K. Low-dose aspirin-induced gastrointestinal diseases: past, present, and future. *J Gastroenterol* 2008; **43**: 581-588 [PMID: 18709479 DOI: 10.1007/s00535-008-2206-5]
- 9 **Yasuda H**, Yamada M, Sawada S, Endo Y, Inoue K, Asano F, Takeyama Y, Yoshida M. Upper gastrointestinal bleeding in patients receiving dual antiplatelet therapy after coronary stenting. *Intern Med* 2009; **48**: 1725-1730 [PMID: 19797827]
- 10 **Cattaneo M**. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1980-1987 [PMID: 15388526]
- 11 **Baigent C**, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioli MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**: 1849-1860 [PMID: 19482214 DOI: 10.1016/S0140-6736(09)60503-1]
- 12 **Berger JS**, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. *Am J Med* 2008; **121**: 43-49 [PMID: 18187072 DOI: 10.1016/j.amjmed.2007.10.002]
- 13 **Yasuda H**. Safety and efficacy of clopidogrel before surgery. (Clinical Medicine Insights Therapeutics 3, 2011). Libertas Academica: Auckland, 2011: 103-111 [DOI: 10.4137/CMT.S2334]
- 14 **Yusuf S**, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494-502 [PMID: 11519503]
- 15 **Mehta SR**, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**: 527-533 [PMID: 11520521]
- 16 **Chan FK**, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, Chan HL, Sung JJ. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001; **344**: 967-973 [PMID: 11274623]
- 17 **Chin MW**, Yong G, Bulsara MK, Rankin J, Forbes GM. Predictive and protective factors associated with upper gastrointestinal bleeding after percutaneous coronary intervention: a case-control study. *Am J Gastroenterol* 2007; **102**: 2411-2416 [PMID: 17850413]
- 18 **Sakamoto C**, Sugano K, Ota S, Sakaki N, Takahashi S, Yoshida Y, Tsukui T, Osawa H, Sakurai Y, Yoshino J, Mizokami Y, Mine T, Arakawa T, Kuwayama H, Saigenji K, Yakabi K, Chiba T,

- Shimosegawa T, Sheehan JE, Perez-Gutthann S, Yamaguchi T, Kaufman DW, Sato T, Kubota K, Terano A. Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal anti-inflammatory drugs in Japan. *Eur J Clin Pharmacol* 2006; **62**: 765-772 [PMID: 16821007]
- 19 **Lanas A**, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011; **9**: 762-768.e6 [PMID: 21699808 DOI: 10.1016/j.cgh.2011.05.020]
 - 20 **Grove EL**, Würtz M, Schwarz P, Jørgensen NR, Vestergaard P. Gastrointestinal events with clopidogrel: a nationwide population-based cohort study. *J Gen Intern Med* 2013; **28**: 216-222 [PMID: 22948933 DOI: 10.1007/s11606-012-2208-0]
 - 21 **Buresly K**, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005; **165**: 784-789 [PMID: 15824298]
 - 22 **Steinhubl SR**, Berger PB, Mann JT, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**: 2411-2420 [PMID: 12435254]
 - 23 **Diener HC**, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364**: 331-337 [PMID: 15276392]
 - 24 **Chen ZM**, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366**: 1607-1621 [PMID: 16271642]
 - 25 **Bhatt DL**, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354**: 1706-1717 [PMID: 16531616]
 - 26 **Abbas AE**, Brodie B, Dixon S, Marsalese D, Brewington S, O'Neill WW, Grines LL, Grines CL. Incidence and prognostic impact of gastrointestinal bleeding after percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2005; **96**: 173-176 [PMID: 16018836]
 - 27 **Hansen ML**, Sørensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsbøll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrøm SZ, Poulsen HE, Køber L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010; **170**: 1433-1441 [PMID: 20837828 DOI: 10.1016/j.jcard.2010.07.027]
 - 28 **Eikelboom JW**, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; **114**: 774-782 [PMID: 16908769]
 - 29 **Nikolsky E**, Stone GW, Kirtane AJ, Dangas GD, Lansky AJ, McLaurin B, Lincoff AM, Feit F, Moses JW, Fahy M, Manoukian SV, White HD, Ohman EM, Bertrand ME, Cox DA, Mehran R. Gastrointestinal bleeding in patients with acute coronary syndromes: incidence, predictors, and clinical implications: analysis from the ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol* 2009; **54**: 1293-1302 [PMID: 19778672 DOI: 10.1016/j.jacc.2009.07.019]
 - 30 **Gaglia MA**, Torguson R, Gonzalez MA, Ben-Dor I, Maluenda G, Collins SD, Syed AI, Delhay C, Wakabayashi K, Belle L, Mahmoudi M, Hanna N, Xue Z, Kaneshige K, Suddath WO, Kent KM, Satler LF, Pichard AD, Waksman R. Correlates and consequences of gastrointestinal bleeding complicating percutaneous coronary intervention. *Am J Cardiol* 2010; **106**: 1069-1074 [PMID: 20920640 DOI: 10.1016/j.amjcard.2010.06.011]
 - 31 **Doyle BJ**, Rihal CS, Gastineau DA, Holmes DR. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol* 2009; **53**: 2019-2027 [PMID: 19477350 DOI: 10.1016/j.jacc.2008.12.073]
 - 32 **Reynolds JD**, Ahearn GS, Angelo M, Zhang J, Cobb F, Stamler JS. S-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. *Proc Natl Acad Sci USA* 2007; **104**: 17058-17062 [PMID: 17940022]
 - 33 **Wu WC**, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; **345**: 1230-1236 [PMID: 11680442]
 - 34 **Villanueva C**, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñoz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368**: 11-21 [PMID: 23281973 DOI: 10.1056/NEJMoa1211801]
 - 35 **Hébert PC**, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409-417 [PMID: 9971864]
 - 36 **Barkun AN**, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, Sinclair P. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; **152**: 101-113 [PMID: 20083829 DOI: 10.7326/0003-4819-152-2-201001190-00009]
 - 37 **Laine L**, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012; **107**: 345-360; quiz 361 [PMID: 22310222 DOI: 10.1038/ajg.2011.480]
 - 38 **Laine L**, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009; **7**: 33-47; quiz 1-2 [PMID: 18986845 DOI: 10.1016/j.cgh.2008.08.016]
 - 39 **Sung JJ**, Lau JY, Ching JY, Wu JC, Lee YT, Chiu PW, Leung VK, Wong VW, Chan FK. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010; **152**: 1-9 [PMID: 19949136 DOI: 10.7326/0003-4819-152-1-201001050-00179]
 - 40 **Valgimigli M**, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012; **125**: 2015-2026 [PMID: 22438530]
 - 41 **Loh JP**, Torguson R, Pendyala LK, Omar A, Chen F, Satler LF, Pichard AD, Waksman R. Impact of early versus late clopidogrel discontinuation on stent thrombosis following percutaneous coronary intervention with first- and second-generation drug-eluting stents. *Am J Cardiol* 2014; **113**: 1968-1976 [PMID: 24767975 DOI: 10.1016/j.amjcard.2014.03.041]
 - 42 **Feres F**, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ, Nicoleta EL, Perin MA, Devito FS, Labrunie A, Salvadori D, Gusmão M, Staico R, Costa JR, de Castro JP, Abizaid AS, Bhatt DL. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013; **310**: 2510-2522 [PMID: 24177257 DOI: 10.1001/jama.2013.282183]
 - 43 **Montalescot G**, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; **373**: 723-731 [PMID: 19249633 DOI: 10.1016/S0140-6736(09)60441-4]
 - 44 **Saito S**, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, Kitagawa K, Nishikawa M, Miyazaki S, Nakamura M. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J* 2014; **78**: 1684-1692 [PMID: 24759796 DOI: 10.1253/

- circj.CJ-13-1482]
- 45 **Dewilde WJ**, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijssen JG, van 't Hof AW, ten Berg JM. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; **381**: 1107-1115 [PMID: 23415013 DOI: 10.1016/S0140-6736(12)62177-1]
 - 46 **Lanas A**, Bajador E, Serrano P, Fuentes J, Carreño S, Guardia J, Sanz M, Montoro M, Sáinz R. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 2000; **343**: 834-839 [PMID: 10995862]
 - 47 **Ng FH**, Chan P, Kwanching CP, Loo CK, Cheung TK, Wong SY, Kng C, Ng KM, Lai ST, Wong BC. Management and outcome of peptic ulcers or erosions in patients receiving a combination of aspirin plus clopidogrel. *J Gastroenterol* 2008; **43**: 679-686 [PMID: 18807129 DOI: 10.1007/s00535-008-2215-4]
 - 48 **Uemura N**, Sugano K, Hiraishi H, Shimada K, Goto S, Uchiyama S, Okada Y, Origasa H, Ikeda Y. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. *J Gastroenterol* 2014; **49**: 814-824 [PMID: 23754512]
 - 49 **Kawai T**, KASHIDA K, Mizokami Y, Matsumoto Y, Oda K, Saito K, Funao N, Nishimura A, Sugano K. TAK-438 Versus Lansoprazole 15 mg for secondary prevention of peptic ulcers associated with low-dose aspirin therapy: results of a phase 3 trial. *Gastroenterol* 2014; **146**: S739 [DOI: 10.1016/S0016-5085(14)62678-0]
 - 50 **Hedberg J**, Sundström J, Thuresson M, Aarskog P, Oldgren J, Bodegard J. Low-dose acetylsalicylic acid and gastrointestinal ulcers or bleeding—a cohort study of the effects of proton pump inhibitor use patterns. *J Intern Med* 2013; **274**: 371-380 [PMID: 23800296 DOI: 10.1111/joim.12103]
 - 51 **Gilard M**, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, Mansourati J, Mottier D, Abgrall JF, Bosch J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; **51**: 256-260 [PMID: 18206732 DOI: 10.1016/j.jacc.2007.06.064]
 - 52 **O'Donoghue ML**, Braunwald E, Antman EM, Murphy SA, Bates ER, Rozenman Y, Michelson AD, Hautvast RW, Ver Lee PN, Close SL, Shen L, Mega JL, Sabatine MS, Wiviott SD. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009; **374**: 989-997 [PMID: 19726078 DOI: 10.1016/S0140-6736(09)61525-7]
 - 53 **Kwok CS**, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; **31**: 810-823 [PMID: 20102352 DOI: 10.1111/j.1365-2036.2010.04247.x]
 - 54 **Agewall S**, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, Huber K, Grove EL, Morais J, Husted S, Wassmann S, Rosano G, Atar D, Pathak A, Kjeldsen K, Storey RF. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013; **34**: 1708-1713 [PMID: 23425521 DOI: 10.1093/eurheartj/ehd042]
 - 55 **Bhatt DL**, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, Shook TL, Lapuerta P, Goldsmith MA, Laine L, Scirica BM, Murphy SA, Cannon CP. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; **363**: 1909-1917 [PMID: 20925534 DOI: 10.1056/NEJMoa1007964]
 - 56 **Wiviott SD**, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001-2015 [PMID: 17982182]
 - 57 **Collet JP**, Hulot JS, Abtan J, Anzaha G, Kerneis M, Silvain J, Cayla G, O'Connor SA, Barthélémy O, Beygui F, Galier S, Brugier D, Stanek EJ, Charland SL, Gallois V, Montalescot G. Prasugrel but not high dose clopidogrel overcomes the lansoprazole neutralizing effect of P2Y12 inhibition: Results of the randomized DOSAPI study. *Eur J Clin Pharmacol* 2014; **70**: 1049-1057 [PMID: 25012577 DOI: 10.1007/s00228-014-1710-1]
 - 58 **Roe MT**, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteza M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367**: 1297-1309 [PMID: 22920930 DOI: 10.1056/NEJMoa1205512]

P- Reviewer: Misra SP, Shah R, Yen HH S- Editor: Ji FF

L- Editor: A E- Editor: Wu HL



Noninvasive ventilation in trauma

Marcin K Karcz, Peter J Papadakos

Marcin K Karcz, Peter J Papadakos, Department of Anesthesiology, University of Rochester, Rochester, NY 14642, United States

Peter J Papadakos, Division of Critical Care Medicine, Departments of Surgery and Neurosurgery, University of Rochester, Rochester, NY 14642, United States

Author contributions: Karcz MK and Papadakos PJ both contributed to this paper.

Conflict-of-interest: Dr. Peter J Papadakos and Dr. Marcin K Karcz have no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Peter J Papadakos, MD, FCCP, FCCM, Director, Division of Critical Care Medicine, Departments of Surgery and Neurosurgery, University of Rochester, 601 Elmwood Avenue, Rochester, NY 14642, United States. peter_papadakos@urmc.rochester.edu
Telephone: +1-585-2752141
Fax: +1-585-2447271

Received: September 29, 2014

Peer-review started: October 2, 2014

First decision: October 28, 2014

Revised: November 3, 2014

Accepted: December 16, 2014

Article in press: December 17, 2014

Published online: February 4, 2015

are at increased risk to develop hypoxemic respiratory failure which may or may not be associated with hypercapnia. Hypoxemia in these patients is due to ventilation perfusion mismatching and right to left shunt because of lung contusion, atelectasis, an inability to clear secretions as well as pneumothorax and/or hemothorax, all of which are common in trauma patients. Noninvasive ventilation has been tried in these patients in order to avoid the complications related to endotracheal intubation, mainly ventilator-associated pneumonia. The potential usefulness of noninvasive ventilation in the ventilatory management of trauma patients, though reported in various studies, has not been sufficiently investigated on a large scale. According to the British Thoracic Society guidelines, the indications and efficacy of noninvasive ventilation treatment in respiratory distress induced by trauma have thus far been inconsistent and merely received a low grade recommendation. In this review paper, we analyse and compare the results of various studies in which noninvasive ventilation was applied and discuss the role and efficacy of this ventilator modality in trauma.

Key words: Acute respiratory distress syndrome; Noninvasive ventilation; Pulmonary contusion; Respiratory failure; Trauma

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Abstract

Trauma patients are a diverse population with heterogeneous needs for ventilatory support. This requirement depends mainly on the severity of their ventilatory dysfunction, degree of deterioration in gaseous exchange, any associated injuries, and the individual feasibility of potentially using a noninvasive ventilation approach. Noninvasive ventilation may reduce the need to intubate patients with trauma-related hypoxemia. It is well-known that these patients

Core tip: The use of noninvasive ventilation is widely recognized as a suitable way to avoid intubation and its associated side effects. Noninvasive ventilation allows increased flexibility in the application and discontinuation of ventilator assistance and preserves airway defense mechanisms. The application of noninvasive ventilation may reduce the need to intubate patients with trauma-related hypoxemia, thereby potentially decreasing intensive care unit length of stay and preventing respiratory complications. In this review article, we summarize the results of various studies in which noninvasive ventilation was applied and discuss the role and efficacy of this ventilator modality in trauma.

Karcz MK, Papadakos PJ. Noninvasive ventilation in trauma. *World J Crit Care Med* 2015; 4(1): 47-54 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/47.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.47>

INTRODUCTION

Nearly one hundred and forty thousand traumatic deaths occur in the United States annually^[1]. The most common cause of death in up to a quarter of patients with multiple system traumas is chest trauma^[2]. Pulmonary contusion is particularly common occurring in approximately seventeen percent of patients with multiple traumas^[3].

Previous studies^[4,5] showed that posttraumatic respiratory failure was caused by an increased amount of interstitial and intraalveolar fluids and described the concept of the so-called "traumatic wet lung", and recommend positive airway pressure by mask to ensure adequate ventilation.

More recently, trauma management has been guided according to the mechanism of injury, its anatomic involvement, and the staging of the injury. Its main aims include pulmonary toilet, control of chest wall pain, surgical stabilization and fluid management. However, ventilator management has received little attention^[6] and this is reflected by a low grade recommendation for the use of noninvasive ventilation in trauma patients by the British Thoracic Society guidelines^[7] and "no recommendation" by Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group^[8] due to a lack of sufficient evidence.

There is a lack of randomized controlled trials on the use of noninvasive ventilation in the trauma population and therefore the efficacy of this treatment in the management of respiratory failure from trauma is for the most part unclear. This review will discuss the current evidence demonstrating the role and efficacy of noninvasive ventilation in trauma.

TRAUMA EPIDEMIOLOGY

The increasing number of high-velocity blunt traumas over the last few decades has caused a progressively higher incidence of chest injuries. As many as seventy to ninety percent of chest injuries in industrialized countries, are caused by blunt trauma, with eighty to ninety percent of cases associated with multiple injuries^[9]. Typical causes of severe chest trauma include high-velocity traumas such as traffic accidents or falls from a height^[10].

Flail chest involves the fracture of three or more ribs in two places or when there are multiple fractures associated with sternal fracture. The clinical significance of this condition varies, depending on the size and location of the flail segment and the extent of the underlying lung contusion. The

respiratory insufficiency associated with flail chest has been shown to be due to the underlying pulmonary contusion rather than paradoxical respiration^[11] and is in fact, the most common injury identified in blunt thoracic trauma.

In severely injured patients with accompanying chest injuries and pulmonary contusion, mortality is reported to be fifteen to sixty percent, depending on the overall severity of the injury^[12]. In comparison, the mortality among patients with isolated chest injuries is low and ranges from zero to five percent in young patients and ten to twenty percent in elderly patients^[13]. Furthermore, pulmonary contusions often occur in the absence of rib fractures^[14].

Three mechanisms that are important in the etiology of pulmonary contusions have been reported^[15]. The "inertial effect" occurs when low-density alveolar tissue is stripped from hilar structures as they accelerate at different rates whereas the "spalling effect" is due to bursting that occurs at the gas-liquid interface. Thirdly, the "implosion effect" involves the overexpansion of gas bubbles after a pressure wave passes and can tear the pulmonary parenchyma.

Pulmonary contusion promotes the development of acute lung injury (ALI), which may progress to acute respiratory distress syndrome (ARDS) secondary to elevated intrapulmonary shunting, ventilation-perfusion mismatching, increased lung water, pulmonary hemorrhage, loss of lung compliance, and the release of cytoactive modulators^[14]. ARDS may develop in as much as five percent of patients with blunt trauma and the major predictors of its development have been shown to be pulmonary contusion and an Injury Severity Score higher than twenty five^[16].

PATHOPHYSIOLOGICAL CONCEPTS OF TRAUMA

The likelihood of complications secondary to severe trauma are the consequences of the direct mechanical damage to the pulmonary parenchyma as well as the indirect systemic and pulmonary sequela. Furthermore, the severity of pulmonary contusion correlates with the development of pulmonary infections, respiratory failure, and mortality^[17] despite the fact that some studies failed to demonstrate a correlation of pulmonary contusion with more severe ALI and ARDS^[18]. This lung injury is an independent risk factor for ALI/ARDS and its severity has been shown to indicate the need for ventilatory support^[16]. Two different forms of posttraumatic ALI/ARDS that have been described universally in trauma patients: (1) early ALI/ARDS which is attributed to hemorrhagic shock and capillary leak and develops within 48 h; and (2) late-onset ALI/ARDS that is associated with a higher incidence of pneumonia, often in conjunction with multiple organ failure^[19].

The lung is exceedingly predisposed to the fracture of blood vessels as well as parenchymal laceration under briskly applied compressive or concussive loads such as those that occur in pulmonary contusions^[14]. Mechanical injuries to the lung can occur through tissue tears when low-density alveolar tissue is stripped from the heavier hilar structures as they accelerate at different rates. The lung can also be damaged by bleeding into distant lung segments, direct laceration of the lung through displacement of fractured ribs and by chest wall compression. The combination of intraparenchymal hemorrhage, edema formation, direct mechanical damage to the lung parenchyma as well as additional indirect injuries, lead to post-traumatic ALI/ARDS.

The infiltration of the lung by polymorphonuclear leukocytes (PMNs) is the most characteristic feature of early post-traumatic ALI/ARDS^[20]. This influx involves PMN retention, margination, and endothelial adhesion within the microvasculature, and migration into the alveolar space and pulmonary interstitium. Subsequently, when the PMNs are activated, they can release numerous cytotoxic products. Hoth *et al.*^[21] showed that the systemic levels of certain chemokines such as monocyte chemoattractant protein-1, macrophage inflammatory protein-2 α (MIP-2 α) and cytokine-induced neutrophil chemoattractant 1 (CINC-1) were significantly elevated at 3 h with all chemokines subsequently found to be significantly elevated at 24 h. Furthermore, the authors showed that pulmonary expression of elastase, CINC-1, tumor necrosis factor- α , interleukin-1 β , intercellular adhesion molecule 1 and MIP-2 α were increased and activated systemic neutrophils demonstrated increased cluster of differentiation molecule 11b. This indicates that the process of innate inflammation is activated both systemically and locally.

Ultimately, the combination of proteases, elastases and reactive oxygen species damage the alveolocapillary barrier, resulting in an increased permeability and in the accumulation of protein-rich alveolar and interstitial edema. This process destabilizes airspaces by inactivating the surfactant of alveoli and terminal airways whose production and function are already significantly impaired^[22]. Eventually, this culminates in a combination of several different clinical phenomena including hypoxemia, ventilation-perfusion mismatching, raised intrapulmonary shunt, and reduced functional capacity.

EVIDENCE-BASED OVERVIEW FOR THE USE OF NONINVASIVE VENTILATION IN TRAUMA

Several systemic reviews and randomized controlled trials have shown the benefits of noninvasive

Table 1 Contraindications to noninvasive ventilation

Trauma, deformity, facial or neurological surgery
Inability to protect airway or cooperate
High risk for aspiration and inability to clear secretions
Upper airway obstruction
Respiratory or cardiac arrest
Organ failure
Unstable cardiac arrhythmia/hemodynamic instability
Severe Encephalopathy (<i>e.g.</i> , GCS < 10)
Severe upper gastrointestinal bleeding

Adapted from ref.^[46]. GCS: Glasgow Comma Scale.

ventilation (NIV) in patients with exacerbation of chronic obstructive pulmonary disease (COPD). These advantages are mostly due to avoidance of invasive mechanical ventilation (IMV) and its complications^[23]. Therefore, NIV in COPD patients with hypercapneic acute respiratory failure (ARF) is now considered a first-line intervention ahead of endotracheal intubation and IMV, providing there are no contraindications to its use (Table 1).

Numerous studies have also shown that the use of NIV in patients with hypoxemic ARF is associated with fewer complications and reduced mechanical ventilation and length of intensive care unit stay^[24]. Those patients who are at high risk of nosocomial infection such as patients with hematological malignancies, with chemotherapy induced neutropenia, organ transplantation recipients as well as the immunosuppressed are likely to benefit from the use of NIV. The Infectious Diseases Society of America and the American Thoracic Society have issued high grade evidence based recommendations in their most recent guidelines for the management and prevention of nosocomial infections thereby advocating the use of NIV whenever appropriate in the management of ARF^[25].

There has been a scarcity of randomized controlled trials on ventilatory management of patients with posttraumatic hypoxemic respiratory failure. The British Thoracic Society has issued a low grade recommendation in its guidelines based on the available level C evidence for the use of NIV in multiple trauma patients^[7]. Similarly, no recommendations were proposed by Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group^[8]. Two recently published systemic reviews^[26,27] have confirmed the insufficiency of the available evidence on this area under discussion. We consequently aimed at investigating the available studies on the indications for NIV in trauma by selecting several major key topics related to pertinent methodological and technical issues.

Our search strategy included data from studies that enrolled adults who developed ARF as a consequence of trauma and who were admitted to the emergency department, trauma service or

Table 2 Tabulated summary of the most significant randomized control studies depicting the use of noninvasive ventilation in posttraumatic hypoxemic respiratory failure

Ref.	No. of Patients enrolled	Study intervention per patient group	Inclusion criteria	Exclusion criteria	Analgesia	Outcomes
Bolliger <i>et al</i> ^[32]	69	36 - CPAP 33 - CPPV	Chest trauma with > 3 rib fractures; Insufficient cough mechanism	PaO ₂ /FiO ₂ < 200	Lumbar epidural catheter	Duration of treatment, ICU length of stay, complications, mortality
Tanaka <i>et al</i> ^[31]	59	25 - CPAP 11 - PSSB 44 - IMV/CMV	Blunt thoracic trauma with flail chest	Flail chest injury caused by CPR	Epidural analgesia	mortality, pulmonary complications
Ferrer <i>et al</i> ^[30]	105	51 - NIV 54 - High-concentration oxygen therapy	Chest trauma with acute respiratory failure	PaCO ₂ > 45 mmHg; need for ETI; recent facial, esophageal, cranial trauma and surgery; ↓ GCS (≤ 11); hemo-dynamic instability; arrhythmia/MI; > 1 organ system failure	Not defined	ICU mortality, rate of intubation, incidence of septic shock
Gunduz <i>et al</i> ^[33]	43	22 - CPAP 21 - IPPV	Flail chest; PaO ₂ /FiO ₂ < 300; Acute respiratory distress	Need for ETI; hemo-dynamic instability; coma/confusion; Emergency surgery	PCA	ICU mortality, complications, improvement in oxygenation, ICU length of stay
Hernandez <i>et al</i> ^[34]	50	25 - NIV 25 - High flow oxygen mask	PaO ₂ /FiO ₂ < 200 for > 8 h while receiving oxygen by high-flow mask	PaCO ₂ > 45 mmHg; need for emergency ETI; standard contraindications for NIV (Table 1); severe traumatic brain injury	Epidural analgesia	Intubation rate Hospital length of stay, Survival

CPAP: Continuous positive airway pressure; CPPV: Continuous positive pressure ventilation; ICU: Intensive care unit; NIV: Noninvasive ventilation; PCA: Patient controlled analgesia; IPPV: Intermittent positive pressure ventilation; CPR: Cardiopulmonary resuscitation; CMV: Continuous mandatory ventilation; IMV: Intermittent mandatory ventilation; PSSB: Pressure support on spontaneous breathing; ETI: Endotracheal intubation; GCS: Glasgow Coma Scale; MI: Myocardial infarction; PaO₂: Partial pressure of O₂ in arterial blood; FiO₂: Inspired oxygen fraction; PaCO₂: Partial pressure of CO₂ in arterial blood.

intensive care unit and consequently treated with NIV. Studies in the pediatric population were excluded. We included randomized controlled trials, as well as observational studies, cohort, case-control and case series from previously published systematic reviews and meta-analyses in our search using MEDLINE and EMBASE, from inception until June 2014. We limited our search to studies on humans and those that were published in English. Our selected keywords were: non-invasive ventilation, continuous positive airway pressure, and trauma. These were cross-referenced with the following search terms: flail chest, pulmonary contusion, chest injury, blunt chest trauma, acute lung injury and acute respiratory distress syndrome. The following discussion is a summary of the most significant studies from our search, depicting the use of noninvasive ventilation in the setting of posttraumatic respiratory failure. Table 2 is a summation of the pertinent randomized controlled studies described below.

In a study by Trinkle *et al*^[11], the possibility that obligatory mechanical ventilation for flail chest was not necessary was first discussed. Their small retrospective review with well-matched cohorts showed that the obligatory ventilation group had a longer hospital stay, a higher mortality and a higher complication rate as compared to a pulmonary contusion (PC) group treated conservatively. In

addition, the PC group averaged only 0.6 ventilator days, indicating that the conservative management was often successful.

Another study by Schweiger *et al*^[28] compared IMV to continuous positive airway pressure (CPAP) in three groups of pigs: a control group, flail chest injury group and pulmonary contusion/flail chest injury group. The authors showed that the use of ten to fifteen centimeters of CPAP was beneficial over IMV alone for correcting alveolar closure thereby minimizing shunt fraction and improving compliance significantly. The need for IMV was significantly reduced after the application of CPAP in all animals with this effect being more pronounced in the pulmonary contusion/flail chest injury group as opposed to the isolated flail chest injury group.

Antonelli *et al*^[29] performed a multicenter survey in 2001, and showed that patients with posttraumatic hypoxemic respiratory failure responded favorably to NIV, with only a moderate failure rate of eighteen percent. The benefit of NIV was attributed to early inclusion of patients with hypoxemia within forty eight hours after trauma, the high prevalence of lung contusions as major underlying cause of hypoxia, and the extended length of NIV use. The authors concluded that in severe thoracic trauma-related hypoxia, early and continuous application of NIV is an effective means

for reducing the need for intubation and shortening the length of intensive care unit stay.

Ferrer *et al.*^[30] carried out a multicenter randomized trial in a mixed population of patients with acute hypoxemic respiratory failure. The authors compared the efficacy of NIV versus breathing with a conventional Venturi oxygen mask at a maximal concentration to avoid intubation and to improve survival. Patients with hypercapnia were excluded. Six patients with thoracic trauma were enrolled in the NIV group vs twelve in the control group. Only one out of six patients in the NIV group required endotracheal intubation vs five out of twelve patients in the control group. No mortality in the intensive care unit was observed in the NIV group as compared to three deaths in the conventional treatment group. Despite the small sample size, the authors did observe a nonsignificant trend in reduction of the intubation rate in patients with thoracic trauma treated with NIV.

In a prospective study by Tanaka *et al.*^[31], the use of CPAP in fifty nine patients with flail chest injury was investigated. The patients in the study were compared to historical controls treated for respiratory failure primarily with mechanical ventilation and the groups were well matched in terms of extent of chest wall injury and overall injury severity. The CPAP group had a lower rate of pulmonary complications and a significantly lower rate of invasive mechanical ventilation use.

Two major randomized controlled trials depicting the use of continuous positive airway pressure in patients with severe chest trauma include one for the prevention and one for treatment of respiratory failure in patients without endotracheal intubation at the time of presentation.

Bolliger *et al.*^[32] randomly allocated patients with multiple rib fractures to two groups in a prevention trial: (1) a CPAP group (thirty six patients) with lumbar epidural buprenorphine or an intercostal nerve block with bupivacaine; and (2) an endotracheal intubation and ventilation group (thirty three patients) with systemic morphine analgesia. Patients included in the study had all of the following: hospital admission within twenty four hours of injury; more than three rib fractures; and insufficient cough mechanism due to pain or pre-existing lung disease. As before, the use of CPAP was compared to intubation and mechanical ventilation. Although the group receiving noninvasive ventilation had a shorter length of stay in the intensive care unit and in hospital, the design of the study was flawed. It did not reflect current clinical practice since endotracheal intubation is not usually used prophylactically for patients similar to those as in this control group. Furthermore one of the exclusion criteria was severe lung contusion. Since no computed tomography chest images had been obtained, it is likely that patients with multiple rib fractures had underlying

pulmonary contusion not detected by plain chest radiographs. On the whole, the two groups were similar at the five percent significance level except for injury severity score which was higher in the intubated group. The authors justified that this was due to the greater number of blunt abdominal injuries in the intubated group, and that the abdominal injuries were considered less severe than the chest injuries in both groups. It was deemed that the difference was not clinically significant.

Gunduz *et al.*^[33] executed a randomized comparison of mask CPAP to intermittent positive pressure ventilation *via* endotracheal intubation in fifty two patients in a treatment study. The results showed that CPAP led to a lower mortality (20% vs 33%, $P < 0.01$) and nosocomial infection rate (18% vs 48%, $P = 0.001$). However, a difference in the length of intensive care unit stay could not be demonstrated and the small number of patients enrolled as well as single-centre design raised concerns regarding generalizability.

Hernandez *et al.*^[34] investigated chest trauma-related hypoxemia and randomized patients to remain on high-flow oxygen mask (twenty five patients) or to receive NIV (twenty five patients) using bi-level positive airway pressure (BiPAP; Respironics Inc.; Murrysville, PA). Patients on oxygen by high-flow mask within the first forty eight hours after thoracic trauma with $\text{PaO}_2/\text{FiO}_2$ ratio less than or equal to two hundred for more than or equal to eight hours were included. The primary end point was intubation and secondary end points length of hospital stay and survival. The protocol utilized for the usage of bi-level positive airway pressure was well outlined, and the intubation criteria were similarly acceptably defined. The study findings showed that the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was higher in the NIV group ($P = 0.02$). It was nonetheless discontinued early due to a significant difference in the intubation rate, in terms of less frequent intubations ($P = 0.02$) and later intubations ($P < 0.01$) in the NIV group. It is therefore evident from the above discussion, that despite the application of NIV over last several decades, there are still insufficient randomized control studies that support its use in trauma patients who have or are at risk for acute respiratory distress or failure.

APPLICATION OF NIV AS A VENTILATION STRATEGY

The diversity of the injuries to the trauma population means that they are especially at high risk of developing ALI/ARDS^[35] and though the management of decreased alveolar ventilation is usually straightforward and is less challenging than that of posttraumatic ALI/ARDS, delayed or inappropriate management may still precipitate

complications.

One of the most important factors contributing to the development of posttraumatic pulmonary complications is atelectasis. Atelectasis causes ventilation-perfusion mismatch and hypoxemia refractory to supplemental oxygen when compensatory mechanisms such as hypoxic pulmonary vasoconstriction become insufficient. The pulmonary and extra-pulmonary damage can potentially lead to increased morbidity and mortality^[36]. Atelectasis also interferes with the clearance of bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Klebsiella pneumoniae*, which are frequent pathogens in early posttraumatic pneumonia^[37,38]. Such a deleterious interaction together with the cyclic recruitment and derecruitment of lung units within atelectatic regions, partly explains why injured patients who frequently present with substantial atelectasis are so prone to develop early nosocomial pneumonia^[39,40].

The identification of patients who should be managed with NIV is challenging, partly because there are few reliable selection criteria. According to the British Thoracic Society guidelines^[7] and the findings of various studies discussed previously, a prudent approach is suggested, and it seems sensible to exclude patients who have multiorgan dysfunction or are poor candidates for NIV by virtue of inability to cooperate or protect the airway or because of excessive secretions (Table 1). NIV should clearly be avoided in patients with shock, severe hypoxemia, or acidosis. A further issue is to agree on a threshold of severity for hypoxemia and acidosis beyond which NIV should be considered as being contraindicated. There are no clear recommendations on this dilemma, and the application of NIV in such patients with posttraumatic ALI/ARDS should be limited to those that are mostly hemodynamically stable or alternatively who can be closely monitored in the intensive care unit, where endotracheal intubation would be promptly available.

The application of optimal levels of NIV can improve oxygenation, relieve dyspnea and dramatically reduce inspiratory muscle effort since patients with posttraumatic ALI/ARDS have diffuse alveolar damage and represent those with the most severe form of hypoxemic respiratory failure^[41]. One has to balance NIV to improve oxygenation on the one hand and increase the pressure support above the CPAP to augment the tidal volume on the other. The clinical endpoints of all these effects are in the diminution of intubation rates.

A reasonable approach would be to use NIV judiciously in trauma patients. Although the optimal duration of the initial NIV trial remains uncertain, a reasonable expectation would be a response within 1 to 4 h of therapy initiation. Patients who are failing an NIV trial should be promptly intubated and mechanically ventilated as any delays in

endotracheal intubation in patients managed with NIV have been associated with decreased survival^[42].

An early conversion to more invasive mechanical ventilation is supported by the finding that the longer atelectasis is tolerated, the higher the transpulmonary pressures required to reinflate them will be. Furthermore, oxygenation goals accepted in some patient populations may not be acceptable in the trauma patient population. Hypoxemia on admission is an independent predictor of poor outcome in these patients which is in contrast to the results of the ARDS Network data. Thus tolerating borderline arterial oxygen tension values such as 55 mmHg can pose a serious threat to patients with cerebral injuries and intracranial hypertension or patients at risk of significant bleeding^[43].

It has been shown that many of these patients deteriorate rapidly on the second or third post-traumatic day, and thus intubation and mechanical ventilation become necessary to ensure adequate oxygenation. This protracted respiratory decompensation corresponds to descriptions of the later-onset ALI/ARDS in trauma victims demonstrating how the coexistence of several predisposing factors may culminate in respiratory failure^[19,44]. Early aggressive mechanical ventilatory support to prevent worsening of arterial oxygenation and progressive atelectasis is therefore recommended by several authors^[12]. Controlled or assisted ventilatory modes can be chosen if patients need to be intubated and ventilated invasively. Putensen *et al.*^[45] described another concept focused on the maintenance of spontaneous breathing stating that diaphragmatic contractions will recruit dependent atelectatic lung regions and in so doing improve both the distribution of ventilation and ventilation-perfusion matching.

In conclusion, despite the heterogeneity of the studies on NIV for the treatment of respiratory failure associated with trauma and the scarcity of available randomized control data, recently published systematic reviews and meta-analysis^[26,27] suggest that NIV could be useful in this setting. It can potentially be associated with a significant reduction in the incidence of overall complications, endotracheal intubation rate, length of intensive care unit stay and mortality. Therefore, the role of NIV in managing respiratory insufficiency associated with trauma may become significant if applied to the properly selected patient at an earlier stage of lung injury by appropriately trained and experienced personnel.

CONCLUSION

The use of NIV is widely recognized as a suitable way to avoid intubation and its associated complications and side effects. NIV allows increased flexibility in the application and discontinuation of ventilator assistance and preserves airway defense

mechanisms as well as speech and swallowing. Ventilatory management in the trauma population however is more challenging because of the difficulty in achieving a balance between the avoidance of further harm to the lungs and sufficient ventilation. Guidelines for the use of NIV in patients with trauma recommend continuous positive airway pressure in those patients who remain hypoxic despite regional anesthesia^[7]. This recommendation is currently rated as low grade, mostly due to the lack of randomized controlled trials in this specific patient population^[6,7]. Given the disappointing results of various trials and meta-analyses^[8], selection of appropriate patients is crucial for optimizing NIV success rates and resource utilization. Extensive application of NIV in trauma-associated ALI/ARDS may otherwise be challenging. Thus, although it has become part of routine care for many patients with acute respiratory failure, implementing NIV for some of them may prove inadequate and may simply prolong the time to an inevitable endotracheal intubation. Close monitoring of its efficacy is therefore mandatory as delaying the time to endotracheal intubation often leads to further respiratory instability. Consequently, patients who do not respond to NIV are burdened by an increased mortality risk when intubation is delayed. The proper identification of patients who are likely to benefit from NIV and simultaneously avoiding the potential complications of a delayed endotracheal intubation remains a challenging issue.

Clinical trials are starting to appear, potentially signaling a reduction in mortality and pulmonary infections based on the less frequent intubations. More research is nonetheless required to determine the role of NIV in respiratory dysfunction stratification with the appropriate inclusion and exclusion criteria. The use of NIV represents one of the goals in investigating the role of ventilatory support to improve outcomes in trauma victims.

REFERENCES

- Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) Online. Atlanta, GA, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention [accessed 2014 August 28]. Available from: URL: <http://www.cdc.gov/injury/wisqars>
- Szucs-Farkas Z, Kaelin I, Flach PM, Roskopf A, Ruder TD, Triantafyllou M, Zimmermann H, Vock P, Bonel HM. Detection of chest trauma with whole-body low-dose linear slit digital radiography: a multireader study. *AJR Am J Roentgenol* 2010; **194**: W388-W395 [PMID: 20410383 DOI: 10.2214/AJR.09.3378]
- Wanek S, Mayberry JC. Blunt thoracic trauma: flail chest, pulmonary contusion, and blast injury. *Crit Care Clin* 2004; **20**: 71-81 [PMID: 14979330 DOI: 10.1016/S0749-0704(03)00098-8]
- Burford TH, BURBANK B. Traumatic wet lung; observations on certain physiologic fundamentals of thoracic trauma. *J Thorac Surg* 1945; **14**: 415-424 [PMID: 21008101]
- Jensen NK. Recovery of pulmonary function after crushing injuries of the chest. *Dis Chest* 1952; **22**: 319-346 [PMID: 12980015 DOI: 10.1378/chest.22.3.319]
- Vidhani K, Kause J, Parr M. Should we follow ATLS guidelines for the management of traumatic pulmonary contusion: the role of non-invasive ventilatory support. *Resuscitation* 2002; **52**: 265-268 [PMID: 11886731 DOI: 10.1016/S0300-9572(01)00475-0]
- British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. *Thorax* 2002; **57**: 192-211 [PMID: 11867822 DOI: 10.1136/thorax.57.3.192]
- Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, Cook DJ, Ayas N, Adhikari NK, Hand L, Scales DC, Pagnotta R, Lazosky L, Rocker G, Dial S, Laupland K, Sanders K, Dodek P. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011; **183**: E195-E214 [PMID: 21324867 DOI: 10.1503/cmaj.100071]
- Karmy-Jones R, Jurkovich GJ, Shatz DV, Brundage S, Wall MJ, Engelhardt S, Hoyt DB, Holcroft J, Knudson MM. Management of traumatic lung injury: a Western Trauma Association Multicenter review. *J Trauma* 2001; **51**: 1049-1053 [PMID: 11740249 DOI: 10.1097/00005373-200112000-00004]
- Richter M, Krettek C, Otte D, Wiese B, Stalp M, Ernst S, Pape HC. Correlation between crash severity, injury severity, and clinical course in car occupants with thoracic trauma: a technical and medical study. *J Trauma* 2001; **51**: 10-16 [PMID: 11468457 DOI: 10.1097/00005373-200107000-00002]
- Trinkle JK, Richardson JD, Franz JL, Grover FL, Arom KV, Holmstrom FM. Management of flail chest without mechanical ventilation. *Ann Thorac Surg* 1975; **19**: 355-363 [PMID: 235908 DOI: 10.1016/S0003-4975(10)64034-9]
- Allen GS, Coates NE. Pulmonary contusion: a collective review. *Am Surg* 1996; **62**: 895-900 [PMID: 8895709]
- Nelson LD. Ventilatory support of the trauma patient with pulmonary contusion. *Respir Care Clin N Am* 1996; **2**: 425-447 [PMID: 9390890]
- Cohn SM. Pulmonary contusion: review of the clinical entity. *J Trauma* 1997; **42**: 973-979 [PMID: 9191684 DOI: 10.1097/00005373-199705000-00033]
- Clemenson CJ. Blast injury. *Physiol Rev* 1956; **36**: 336-354 [PMID: 13359127]
- Miller PR, Croce MA, Kilgo PD, Scott J, Fabian TC. Acute respiratory distress syndrome in blunt trauma: identification of independent risk factors. *Am Surg* 2002; **68**: 845-850; discussion 850-851 [PMID: 12412708]
- Miller PR, Croce MA, Bee TK, Qaisi WG, Smith CP, Collins GL, Fabian TC. ARDS after pulmonary contusion: accurate measurement of contusion volume identifies high-risk patients. *J Trauma* 2001; **51**: 223-228; discussion 229-230 [PMID: 11493778 DOI: 10.1097/00005373-200108000-00003]
- Dicker RA, Morabito DJ, Pittet JF, Campbell AR, Mackersie RC. Acute respiratory distress syndrome criteria in trauma patients: why the definitions do not work. *J Trauma* 2004; **57**: 522-526; discussion 526-528 [PMID: 15454797 DOI: 10.1097/01.TA.0000135749.64867.06]
- Croce MA, Fabian TC, Davis KA, Gavin TJ. Early and late acute respiratory distress syndrome: two distinct clinical entities. *J Trauma* 1999; **46**: 361-366; discussion 366-368 [PMID: 10088834 DOI: 10.1097/00005373-199903000-00001]
- Pallister I, Dent C, Topley N. Increased neutrophil migratory activity after major trauma: a factor in the etiology of acute respiratory distress syndrome? *Crit Care Med* 2002; **30**: 1717-1721 [PMID: 12163782 DOI: 10.1097/00003246-200208000-00007]
- Hoth JJ, Stitzel JD, Gayzik FS, Brownlee NA, Miller PR, Yoza BK, McCall CE, Meredith JW, Payne RM. The pathogenesis of pulmonary contusion: an open chest model in the rat. *J Trauma* 2006; **61**: 32-44; discussion 44-45 [PMID: 16832247 DOI: 10.1097/01.ta.0000224141.69216.aa]
- Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Fowler AA, Hudson LD, Maunder RJ, Crim C, Hyers TM. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991; **88**: 1976-1981 [PMID: 1752956 DOI: 10.1172/JCI115523]
- Keenan SP, Sinuff T, Cook DJ, Hill NS. Does noninvasive positive

- pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. *Crit Care Med* 2004; **32**: 2516-2523 [PMID: 15599160 DOI: 10.1097/01.CCM.0000148011.51681.E2]
- 24 **Brochard L.** Noninvasive ventilation for acute respiratory failure. *JAMA* 2002; **288**: 932-935 [PMID: 12190351 DOI: 10.1001/jama.288.8.932]
 - 25 **American Thoracic Society, Infectious Diseases Society of America.** Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388-416 [PMID: 15699079 DOI: 10.1164/rccm.200405-644ST]
 - 26 **Chiumello D, Coppola S, Froio S, Gregoretti C, Consonni D.** Noninvasive ventilation in chest trauma: systematic review and meta-analysis. *Intensive Care Med* 2013; **39**: 1171-1180 [PMID: 23571872 DOI: 10.1007/s00134-013-2901-4]
 - 27 **Duggal A, Perez P, Golan E, Tremblay L, Sinuff T.** Safety and efficacy of noninvasive ventilation in patients with blunt chest trauma: a systematic review. *Crit Care* 2013; **17**: R142 [PMID: 23876230 DOI: 10.1186/cc12821]
 - 28 **Schweiger JW, Downs JB, Smith RA.** Chest wall disruption with and without acute lung injury: effects of continuous positive airway pressure therapy on ventilation and perfusion relationships. *Crit Care Med* 2003; **31**: 2364-2370 [PMID: 14501968 DOI: 10.1097/01.CCM.0000085187.36136.9B]
 - 29 **Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU.** Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001; **27**: 1718-1728 [PMID: 11810114 DOI: 10.1007/s00134-001-1114-4]
 - 30 **Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A.** Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; **168**: 1438-1444 [PMID: 14500259 DOI: 10.1164/rccm.200301-072OC]
 - 31 **Tanaka H, Tajimi K, Endoh Y, Kobayashi K.** Pneumatic stabilization for flail chest injury: an 11-year study. *Surg Today* 2001; **31**: 12-17 [PMID: 11213036 DOI: 10.1007/s005950170213]
 - 32 **Bolliger CT, Van Eeden SF.** Treatment of multiple rib fractures. Randomized controlled trial comparing ventilatory with nonventilatory management. *Chest* 1990; **97**: 943-948 [PMID: 2182301 DOI: 10.1378/chest.97.4.943]
 - 33 **Gunduz M, Unlugenc H, Ozalevli M, Inanoglu K, Akman H.** A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J* 2005; **22**: 325-329 [PMID: 15843697 DOI: 10.1136/emj.2004.019786]
 - 34 **Hernandez G, Fernandez R, Lopez-Reina P, Cuena R, Pedrosa A, Ortiz R, Hiradier P.** Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. *Chest* 2010; **137**: 74-80 [PMID: 19749006 DOI: 10.1378/chest.09-1114]
 - 35 **Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A.** Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med* 2005; **31**: 922-926 [PMID: 15856172 DOI: 10.1007/s00134-005-2625-1]
 - 36 **Squadrone V, Coia M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G, Vilianis G, Fiore G, Cavallo F, Ranieri VM.** Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA* 2005; **293**: 589-595 [PMID: 15687314 DOI: 10.1001/jama.293.5.589]
 - 37 **van Kaam AH, Lachmann RA, Herting E, De Jaegere A, van Iwaarden F, Noorduyn LA, Kok JH, Haitsma JJ, Lachmann B.** Reducing atelectasis attenuates bacterial growth and translocation in experimental pneumonia. *Am J Respir Crit Care Med* 2004; **169**: 1046-1053 [PMID: 14977624 DOI: 10.1164/rccm.200312-1779OC]
 - 38 **Croce MA, Fabian TC, Mueller EW, Maish GO, Cox JC, Bee TK, Boucher BA, Wood GC.** The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. *J Trauma* 2004; **56**: 931-934; discussion 934-936 [PMID: 15179229 DOI: 10.1097/01.TA.0000127769.29009.8C]
 - 39 **Croce MA, Fabian TC, Waddle-Smith L, Maxwell RA.** Identification of early predictors for post-traumatic pneumonia. *Am Surg* 2001; **67**: 105-110 [PMID: 11243529]
 - 40 **Duggan M, Kavanagh BP.** Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology* 2005; **102**: 838-854 [PMID: 15791115 DOI: 10.1097/00000542-200504000-00021]
 - 41 **L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, Mancebo J, Brochard L.** Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med* 2005; **172**: 1112-1118 [PMID: 16081548 DOI: 10.1164/rccm.200402-226OC]
 - 42 **Festic E, Gajic O, Limper AH, Aksamit TR.** Acute respiratory failure due to pneumocystis pneumonia in patients without human immunodeficiency virus infection: outcome and associated features. *Chest* 2005; **128**: 573-579 [PMID: 16100140 DOI: 10.1378/chest.128.2.573]
 - 43 **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.** *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
 - 44 **Regel G, Grotz M, Weltner T, Sturm JA, Tschern H.** Pattern of organ failure following severe trauma. *World J Surg* 1996; **20**: 422-429 [PMID: 8662130 DOI: 10.1007/s002689900067]
 - 45 **Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, Von Spiegel T, Mutz N.** Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001; **164**: 43-49 [PMID: 11435237 DOI: 10.1164/ajrcm.164.1.2001078]
 - 46 **Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Française, and approved by ATS Board of Directors, December 2000.** International Consensus Conferences in Intensive Care Medicine: Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure. *Am J Respir Crit Care Med* 2001; **163**: 283-291 [PMID: 11208659 DOI: 10.1164/ajrcm.163.1.ats100]

P- Reviewer: Czaplik M, Hsu CW, Kuan YH, Willms D
S- Editor: Song XX L- Editor: A E- Editor: Wu HL



Checklist for early recognition and treatment of acute illness: International collaboration to improve critical care practice

Marija Vukoja, Rahul Kashyap, Srdjan Gavrilovic, Yue Dong, Oguz Kilickaya, Ognjen Gajic

Marija Vukoja, Srdjan Gavrilovic, The Institute for Pulmonary Diseases of Vojvodina Sremska Kamenica, Faculty of Medicine, University of Novi Sad, Sremska Kamenica 21204, Serbia

Rahul Kashyap, Yue Dong, Ognjen Gajic, Mayo Clinic, Rochester, MN 55905, United States

Oguz Kilickaya, Gulhane Military Medical Faculty, 6400 Ankara, Turkey

Author contributions: All listed authors contributed to the design, conception and writing of this paper; the CERTAIN investigators contributed to the development and implementation of CERTAIN in various ICU settings.

Conflict-of-interest: This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic conflict of interest policies. Mayo Clinic and Dr Gajic hold intellectual property rights and financial conflict of interest in critical care related software tools.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Marija Vukoja, MD, PhD, The Institute for Pulmonary Diseases of Vojvodina Sremska Kamenica, Faculty of Medicine, University of Novi Sad, Put doktora Goldmana 4, 21204 Sremska Kamenica, Serbia. kojicic.marija@gmail.com
Telephone: +381-21-4805202

Fax: +381-21-527960

Received: August 23, 2014

Peer-review started: August 24, 2014

First decision: November 27, 2014

Revised: December 19, 2014

Accepted: January 18, 2015

Article in press: January 20, 2015

Published online: February 4, 2015

care delivery is likely to minimize preventable death, disability and costly complications for any healthcare system's sickest patients, but no large-scale efforts have so far been undertaken towards these goals. The advances in medical informatics and human factors engineering have provided possibility for novel and user-friendly clinical decision support tools that can be applied in a complex and busy hospital setting. To facilitate timely and accurate best-practice delivery in critically ill patients international group of intensive care unit (ICU) physicians and researchers developed a simple decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN). The tool has been refined and tested in high fidelity simulated clinical environment and has been shown to improve performance of clinical providers faced with simulated emergencies. The aim of this international educational intervention is to implement CERTAIN into clinical practice in hospital settings with variable resources (included those in low income countries) and evaluate the impact of the tool on the care processes and patient outcomes. To accomplish our aims, CERTAIN will be uniformly available on either mobile or fixed computing devices (as well as a backup paper version) and applied in a standardized manner in the ICUs of diverse hospitals. To ensure the effectiveness of the proposed intervention, access to CERTAIN is coupled with structured training of bedside ICU providers.

Key words: Decision support systems; Critical care; Education; Checklists; Medical informatics

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Important barriers including limited access to educational resources, geographical distance, cost and lack of efficient global infrastructure greatly limit the feasibility of on site educational interventions. To overcome these barriers the international group of

Abstract

Processes to ensure world-wide best-practice for critical

intensive care unit (ICU) physicians and researchers developed a simple decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN). CERTAIN is a systematic approach to error prevention with the use of checklists and electronic decision support algorithms. The effectiveness of CERTAIN to improve outcomes and reduce costs will be tested in a stepped wedge cluster before-after trial in ICUs with variable resources across five continents.

Vukoja M, Kashyap R, Gavrilovic S, Dong Y, Kilickaya O, Gajic O. Checklist for early recognition and treatment of acute illness: International collaboration to improve critical care practice. *World J Crit Care Med* 2015; 4(1): 55-61 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/55.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.55>

INTRODUCTION

Incomplete knowledge of best practices by front-line health care providers and delayed, error-prone delivery processes can offset the potential benefits of critical care support. This is particularly important early in the course of critical illness, when errors and delays in appropriate care often lead to costly complications and poor outcomes, even in advanced hospitals^[1,2]. Three major barriers prevent adequate delivery of care for critically ill patients: (1) provider (rather than patient)-oriented care delivery; (2) lack of access to standardized decision support; and (3) lack of an efficient global infrastructure. To overcome these barriers there is a need for standardized approach to evaluation and treatment of critically ill patients^[3,4]. The systematic approach to error prevention with the use of checklists has been proposed to improve patient safety in surgical settings and in intensive care units (ICUs) in developed countries with encouraging results^[5-9]. The expected benefit from a checklist approach to quality improvement process in various hospital settings including low-and middle-income countries is likely to be high. Indeed, the impact of surgical safety checklist was even more pronounced in the low-income country hospitals^[5,10]. Our recent survey on critical care practices in resource limited settings showed that majority of these ICUs do not use any kind of checklist for acute resuscitation or rounding^[11]. To address the third barrier, there is a need to establish an efficient interdisciplinary collaboration and robust infrastructure.

The advances in medical informatics and human factors engineering have provided possibility for novel and user friendly clinical decision support (CDS) tools that can be applied in a complex and busy hospital setting^[12-14]. To facilitate timely and improved best-practice delivery and a reduction in preventable death and complications in critically ill

patients compared to current practice international group of ICU physician and researchers developed a simple electronic decision support tool: Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN)^[15,16]. The central hypothesis is that health care provider access and training in CERTAIN will facilitate timely and accurate best-practice delivery and improve outcomes of critically ill patients.

OVERVIEW OF STUDY DESIGN

The Primary Objectives of the CERTAIN Study are: (1) to iteratively refine electronic decision support tool (CERTAIN); and (2) to implement CERTAIN into clinical practice in variable hospital settings and evaluate the impact of the tool on the care processes and patient outcomes.

The Secondary objective is to implement CERTAIN into educational settings as an interactive electronic educational tool.

The key outcomes of interest are related to better care, and better health at a lower cost (see below).

To ensure the effectiveness of the proposed intervention, access to the easy to use electronic checklist/decision support (CERTAIN) will be coupled with structured training of bedside ICU providers. CERTAIN will be uniformly available on either mobile or fixed computing devices (as well as a backup paper version). The proposed project consists of two phases.

PHASE 1 (TOOL REFINEMENT)

Description of the novel technology

CERTAIN is a web-based decision support tool displaying relevant clinical information incorporated with the knowledge about evidence-based best clinical practices, which are organized according to a systematic review of end user data needs and ergonomic workflow^[17].

CERTAIN is a web based application suite hosting in a secured Platform as a Service (PaaS) environment with on-demanding scalability up to multiple Linux servers. Current main version graphical user interface (GUI) is developed by using Adobe ActionScript 3 which could be viewed through any web browser including flash player either from regular computer (desktop/laptop) or from mobile devices (tablet pc, smartphone). A mobile app version which is developed by HTML5 is also provided as a complementary part to extend CERTAIN availability and better user experience on the mobile device. A backup paper version is available in a case of problems with internet connection.

CERTAIN modules

CERTAIN consists of two modules, stabilization (admission/resuscitation) module [CERTAIN evaluation of life threatening emergencies (ELITE)] and

Figure 1 CERTAIN-ELITE (Evaluation of Life Threatening Emergencies) admission/resuscitation module. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness; ELITE: Evaluation of life threatening emergencies.

rounding module (CERTAIN Rounds), to help the clinicians with the routine recommended care processes which need to be assessed daily for every patient.

Stabilization (Admission/resuscitation) module

CERTAIN-ELITE (Figure 1) is designed as an electronic choreography for evaluation of life-threatening emergencies with embedded timer, checklist and decision support cards to facilitate error-free care of acutely deteriorating patient (ICU admission and subsequent emergencies).

In CERTAIN data elements are organized by considering how experts incorporate information into decision making mental models. Reading from up to bottom organizational elements are (1) primary (ABCDE) survey; and (2) secondary patient survey, and from left to right the key organizational elements are: (1) clinical context -reason for admission/patient problem list; (2) provider actions tracked in the status central panel; and (3) proposed medications and interventions.

Optimization (Rounding) module

CERTAIN Rounding module (Figure 2) is designed as a simple and efficient ICU rounding tool with embedded checklist and decision support cards to facilitate error-free day-to-day care in the ICU.

The key characteristics of CERTAIN are: (1)

task specific, concept-oriented views of patient data -CERTAIN serves to organize appropriate data determined by a systematic review of end user data needs; (2) knowledge translation - evidence based checklists are incorporated; (3) collaborative workspace - real time plan of care with patient specific tasks, status checks and reminders which provide a location to communicate clearly the goals of care and their status to all members of the multidisciplinary team; (4) reports - scheduled and on demand unit/hospital level reports of quality metrics can be designed for local reporting; and (5) user interface - providers will interact with the system through secure fixed and mobile computer interfaces.

Supporting evidence base

Components of the evidence-informed ICU care practices incorporated in CERTAIN decision support cards are informed by a systematic, comprehensive search for published guidelines, clinical trials and cohort studies in multiple databases such as Medline, EMBASE, National Guideline Clearing House, and Cochrane Library. The guidelines and clinical studies are critically appraised to identify practices with the best evidence.

Utility of CERTAIN has been evaluated in high fidelity clinical simulation setting and has been shown to improve performance of clinical providers faced with simulated emergencies. Among 18 providers

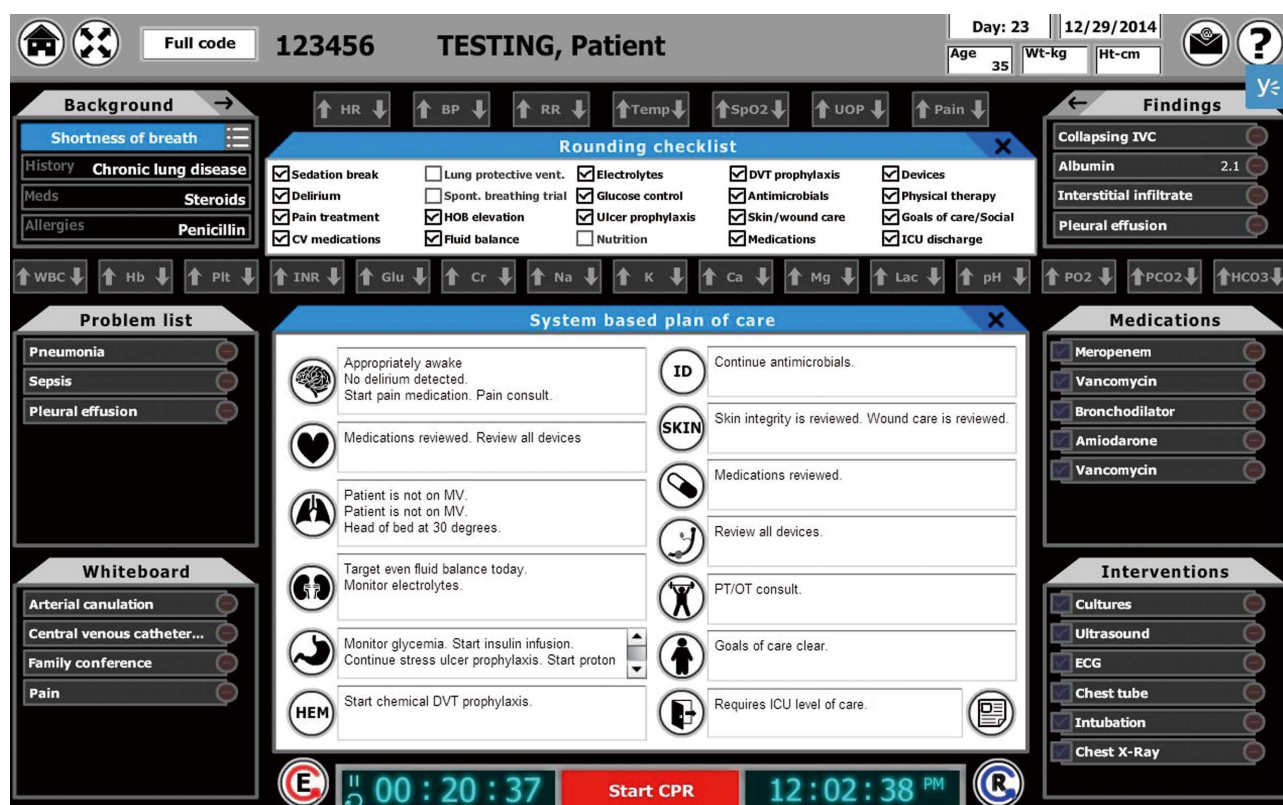


Figure 2 Rounding module with system based plan of care and rounding checklists.

there was 14% absolute reduction in omissions of critical tasks with CERTAIN. Most providers (72%) felt better prepared during an emergency scenario when using the CERTAIN model^[18].

Following initial development and alpha testing at Mayo Clinic simulation center the tool has been further refined by: (1) web-based survey of decision support needs in an international convenience sample of critical care practitioners from various backgrounds and settings. By directly requesting acute care providers to rank the importance of guidelines and information detailed in literature (from high to low priority), we defined and developed a card template. The detailed description of the development of card template can be found elsewhere^[19]; and (2) a decision support card was made for each clinical problem, medication or intervention and was then validated through a modified Delphi process by multidisciplinary, international European Society of Critical Care Medicine/American Thoracic Society/The United States Critical Illness and Injury Trials Group (ESICM/ATS/USCIITG) (ESICM/ATS/USCIITG) expert panel. Once the card was validated, each card is assigned expiration date for ensuring up to date medical knowledge.

PHASE 2 IMPLEMENTATION OF CERTAIN

Participant recruitment and enrollment

Settings: Following IRB approval the effectiveness of CERTAIN to improve outcomes and reduce costs

will be tested in a stepped wedge cluster before-after trial of a total of 25-40 ICUs in hospitals with variable resources from five continents (Asia, Africa, Europe, America, Australia) (Figure 3). Total of 12000-15000 patients will be included in the study (Figure 4).

Study subjects: All adult (≥ 18 years) patients admitted for the first time to the participating ICUs will be included.

Not critically ill, admitted for low risk monitoring, planned ICU admissions for routine postoperative surveillance for less than 24 h after uncomplicated surgery, readmission and transferred from outside ICU.

Data collection for outcome assessment: The pre-implementation phase consists of 3 mo full dataset, prospectively and 9 previous months of minimal outcome data, retrospectively baseline data collection (up to 250 patients per ICU). Data collection will include epidemiological data and daily assessment of processes of care, organ function and support. Length of ICU and hospital stay and outcome will be collected. The site research coordinators are instructed in the study protocol, outcome measures, and data collection process as soon as IRB approval is obtained.

Following pre-implementation phase and prior to the clinical implementation and testing, local champions resuscitation skills will be evaluated by

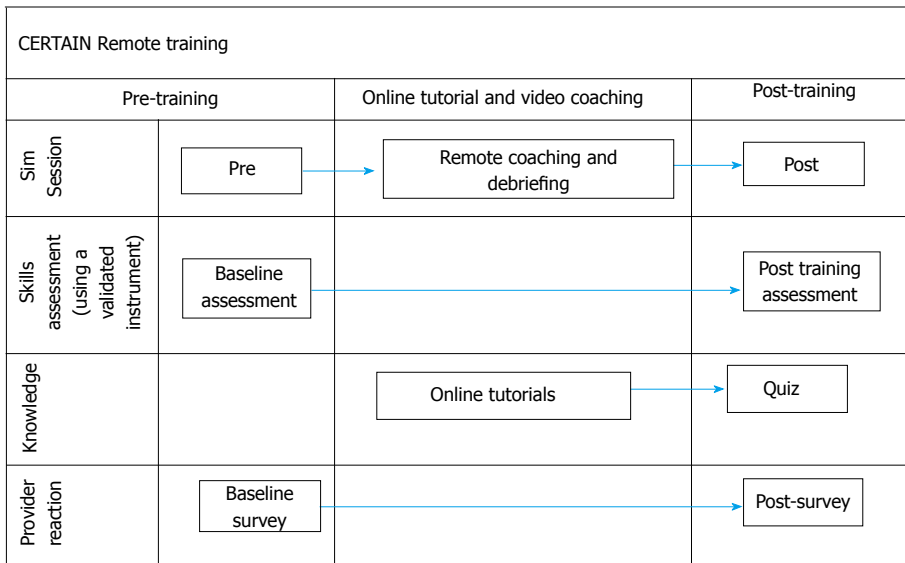


Figure 3 CERTAIN remote simulation training flow. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness.

remote online video simulation assessment (in a simulated acute care environment of all participating centers) (Figure 3). Each center has a baseline assessment with three physicians (Implementation team) who are given three admission and one rounding scenarios. Following baseline session, the participating centers will be given access to online CERTAIN tool and training materials. After 2-4 wk a follow up training session is performed during which we will test competency of the participants to use the CERTAIN tool. Again, the physicians are given 3 admission and one rounding scenario similar to the baseline session, but this time the physicians will use CERTAIN during all scenarios. These practice scenarios will be followed with remote debriefing to provide structured feedback to enhance learning experience. Following successful second skill assessment, the Implementation team will be certified and use the similar simulation procedure on site to train local staff with local languages. Once local physicians and nurses complete the training program the participating center will have a permission to proceed to clinical implementation and testing.

Bedside ICU providers (physicians and nurses) will be given access to and training in CERTAIN starting with the single ICU bed in a PILOT ICU with subsequent expansion to the whole unit followed by the step-wedge implementation in a similar manner across international ICUs. The participating site clinicians will be trained in the use of CERTAIN by the local Implementation teams. During the process, adoption feedback and suggestion will be collected by design team and make necessary customization for local hospitals. The local implementation experience will also be shared with whole CERTAIN investigators to facilitate subsequent implementation efforts in other centers.

Data collection on outcomes measures and

compliance with each element of best practices will be done daily during the control period by trained research coordinators. It consists of 6 mo full dataset, and 6 more months of minimal outcome data; up to 250 patients per ICU. After implementation of CERTAIN during the post-intervention period, enrollment tracking, data cleaning, outcome assignment, outcome validation, and outcome tracking will be performed electronically. The site research coordinators will be trained in the study protocol, outcome measures, and data collection process *via* webinars conducted by the Outcomes group.

OUTCOME ASSESSMENT

We will track relevant outcomes to demonstrate better care, better health and lower costs in the objectives as outlined below: (1) with regards to better care: we expect to see an improvement in the processes of care, safety culture and patient and family satisfaction. Specifically we will measure: Compliance with timely and adequate antimicrobial therapy; Compliance with ventilator bundle (DVT prophylaxis, GI prophylaxis, sedation holidays, assessment of readiness to extubate); Compliance with lung-protective mechanical ventilation; Conservative blood product usage; (2) better health: we will examine the health outcomes of patients in a number of ways. Measures include: ICU, hospital and 28 d mortality, and discharge disposition (home vs other institution); and (3) lower costs - Resource utilization: ICU and hospital length of stay.

CONFIDENTIALITY OF SUBJECTS' DATA AND DATA SECURITY

All the cloud servers and database services used in CERTAIN project are secured by adopting Server

	Year 1	Year 2	
Hospital 1 (PILOT)	Systematic review of best practice Refine prototype	Customization based on local needs	Identification of local champion
Hospital 2			Implementation of CERTAIN
Hospital 3			Implementation of CERTAIN
Hospital 4			Implementation of CERTAIN
Hospital X			Implementation of CERTAIN
All Hospitals	Define, design, implement, validate and maintain key data entry to the cloud environment in support of clinical utilization of CERTAIN		

Figure 4 Overview of the proposed intervention. CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness.

Name Indication (SNI) based Secure Sockets Layer (SSL) protocol. Every request to the server required to be authenticated by our SSL certificate. The data stored in the Database are encrypted based on security requirements and every hospital has its own separated logical space. Data backup is also planned and implemented by setting up scheduled jobs in the server side.

Each study subject will be assigned a unique study identification number linked to his or her medical record number at the respective home site. We will use existing procedures to ensure that individual patient identifiers are kept separate from analysis files and are available only to project personnel on a need-to-know basis. All identified patient data necessary to complete this research will be created and stored in secure computers to which only project team members will have access. Only project personnel directly involved in the study will have access to identified patient data and medical charts at their respective site. All project personnel with access to patient data will be trained in the proper handling of such data.

LIMITATIONS

Restricted availability of some medications and equipment in resource-limited settings may pre-

clude delivery of best care practices and limit generalizability of the study results. Nevertheless, we expect to see improvement in all proposed outcomes with the implementation of the CERTAIN tool. We overcame possible lack of internet access by providing paper version of the tool.

CONCLUSION

CERTAIN initiative directly addresses the major barriers to the consistent and timely delivery of error-free, evidence-informed clinical care to critically ill patients by: (1) organizing clinical information into vital components specific to the patient's condition and task at hand; (2) incorporating centralized CDS tools informed by evidence-based guidelines that are both patient and context appropriate to ensure that interventions are implemented at the right time for the right patients for the right conditions; (3) coupling the intervention with an interactive educational initiative to decrease the gap between knowledge and translation to clinical practice; and (4) providing centralized, timely and regular compliance and quality metrics feedback and auditing to empower institutions to implement and enact change. By providing ready solutions for major barriers - lack of collaboration, early recognition, prompting and support tools - we propose to be able to increase access to critical care knowledge at the point of care thereby minimizing diagnostic error, therapeutic harm and resulting preventable death, disability and cost.

REFERENCES

- 1 **Moreno RP**, Rhodes A, Donchin Y. Patient safety in intensive care medicine: the Declaration of Vienna. *Intensive Care Med* 2009; **35**: 1667-1672 [PMID: 19697007]
- 2 **Bracco D**, Favre JB, Bissonnette B, Wasserfallen JB, Revelly JP, Ravussin P, Chioléro R. Human errors in a multidisciplinary intensive care unit: a 1-year prospective study. *Intensive Care Med* 2001; **27**: 137-145 [PMID: 11280625 DOI: 10.1007/s001340000751]
- 3 **Pronovost PJ**, Berenholtz SM, Ngo K, McDowell M, Holzmueller C, Haraden C, Resar R, Rainey T, Nolan T, Dorman T. Developing and pilot testing quality indicators in the intensive care unit. *J Crit Care* 2003; **18**: 145-155 [PMID: 14595567 DOI: 10.1016/j.jcrc.2003.08.003]
- 4 **Ilan R**, Fowler RA, Geerts R, Pinto R, Sibbald WJ, Martin CM. Knowledge translation in critical care: factors associated with prescription of commonly recommended best practices for critically ill patients. *Crit Care Med* 2007; **35**: 1696-1702 [PMID: 17522582]
- 5 **Haynes AB**, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, Herbosa T, Joseph S, Kibatala PL, Lapitan MC, Merry AF, Moorthy K, Reznick RK, Taylor B, Gawande AA. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009; **360**: 491-499 [PMID: 19144931]
- 6 **Arriaga AF**, Bader AM, Wong JM, Lipsitz SR, Berry WR, Ziewacz JE, Hepner DL, Boorman DJ, Pozner CN, Smink DS, Gawande AA. Simulation-based trial of surgical-crisis checklists. *N Engl J Med* 2013; **368**: 246-253 [PMID: 23323901]
- 7 **de Vries EN**, Dijkstra L, Smorenburg SM, Meijer RP, Boermeester MA. The SURgical PATient Safety System (SURPASS) checklist optimizes timing of antibiotic prophylaxis. *Patient Saf Surg* 2010; **4**:

- 6 [PMID: 20388204]
- 8 **Gawande A.** The checklist manifesto: how to get things right. 1st ed. New York: Metropolitan Books, 2010
- 9 **Treadwell JR,** Lucas S, Tsou AY. Surgical checklists: a systematic review of impacts and implementation. *BMJ Qual Saf* 2014; **23**: 299-318 [PMID: 23922403 DOI: 10.1136/bmjqs-2012-001797]
- 10 **Kwok AC,** Funk LM, Baltaga R, Lipsitz SR, Merry AF, Dziekan G, Ciobanu G, Berry WR, Gawande AA. Implementation of the World Health Organization surgical safety checklist, including introduction of pulse oximetry, in a resource-limited setting. *Ann Surg* 2013; **257**: 633-639 [PMID: 23207242 DOI: 10.1097/SLA.0b013e3182777fa4]
- 11 **Vukoja M,** Riviello E, Gavrilovic S, Adhikari NKJ, Kashyap R, Bhagwanjee S, Gajic O, Kilickaya O. A Survey on Critical Care Resources and Practices in Low- and Middle-Income Countries. *Global Heart* 2014; **9**: 337-342.e5 [DOI: 10.1016/j.ghart.2014.08.002]
- 12 **Herasevich V,** Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. *Mayo Clin Proc* 2010; **85**: 247-254 [PMID: 20194152 DOI: 10.4065/mcp.2009.0479]
- 13 **Pickering BW,** Herasevich V, Ahmed A, Gajic O. Novel Representation of Clinical Information in the ICU: Developing User Interfaces which Reduce Information Overload. *Appl Clin Inform* 2010; **1**: 116-131 [PMID: 23616831 DOI: 10.4338/ACI-2009-12-CR-0027]
- 14 **Pickering BW,** Litell JM, Herasevich V, Gajic O. Clinical review: the hospital of the future - building intelligent environments to facilitate safe and effective acute care delivery. *Crit Care* 2012; **16**: 220 [PMID: 22546172 DOI: 10.1186/cc11142]
- 15 **CERTAIN -Checklist for Early Recognition and Treatment of Acute Illness.** Cited 2014. Available from: URL: <http://www.icertain.org/>
- 16 **Baker T.** The Certain Project (2013) European Society of Critical Care Medicine (ESICM). Cited 2013-12. Available from: URL: <http://www.esicm.org/upload/530c4acfcfa7c-escim-globalintensivecareworkinggroup-projects-022014.pdf>
- 17 **Pickering BW,** Gajic O, Ahmed A, Herasevich V, Keegan MT. Data utilization for medical decision making at the time of patient admission to ICU. *Crit Care Med* 2013; **41**: 1502-1510 [PMID: 23528804 DOI: 10.1097/CCM.0b013e318287f0c0]
- 18 **Sevilla-Berrios R,** O'Horo J, Schmickl C, Erdogan A, Chen X, Garcia Arguello L, Dong Y, Gajic O. Prompting with Electronic Checklist Improves Clinician Performance in Medical Emergencies: High Fidelity Simulation Study. *Critical Care Medicine* 2014; **42**: A1424 [DOI: 10.1097/01.ccm.0000457761.97547.2e]
- 19 **Bonneton BA,** Adhikari N, Schultz M, Kilickaya O, Senkal S, Gavrilovic Srdjan, Kashyap R, Pickering B. Development of bedside decision support cards based on the information needs of acute care providers. *Critical Care Medicine* 2013; **41**: A30-A31 [DOI: 10.1097/01.ccm.0000439294.37718.0e]

P- Reviewer: John J, Yao YM **S- Editor:** Tian YL **L- Editor:** A
E- Editor: Wu HL



Has Stewart approach improved our ability to diagnose acid-base disorders in critically ill patients?

Fabio D Masevicius, Arnaldo Dubin

Fabio D Masevicius, Arnaldo Dubin, Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Buenos Aires C1115AAB, Argentina
Arnaldo Dubin, Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, 1900 La Plata, Argentina

Author contributions: Both authors contributed to this work.

Conflict-of-interest: The authors have no conflict of interest to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Arnaldo Dubin, MD, PhD, Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Azcuénaga 870, C1115AAB Ciudad Autónoma de Buenos Aires, Argentina. arnaldodubin@gmail.com

Telephone: +54-91-150102431

Received: September 25, 2014

Peer-review started: September 28, 2014

First decision: December 17, 2014

Revised: December 29, 2014

Accepted: January 15, 2015

Article in press: January 19, 2015

Published online: February 4, 2015

Abstract

The Stewart approach-the application of basic physical-chemical principles of aqueous solutions to blood-is an appealing method for analyzing acid-base disorders. These principles mainly dictate that pH is determined by three independent variables, which change primarily and independently of one other. In blood plasma in vivo these variables are: (1) the PCO_2 ; (2) the strong ion difference (SID)-the difference between the sums of all the strong (*i.e.*, fully dissociated, chemically nonreacting) cations and all the strong anions; and (3)

the nonvolatile weak acids (A_{tot}). Accordingly, the pH and the bicarbonate levels (dependent variables) are only altered when one or more of the independent variables change. Moreover, the source of H^+ is the dissociation of water to maintain electroneutrality when the independent variables are modified. The basic principles of the Stewart approach in blood, however, have been challenged in different ways. First, the presumed independent variables are actually interdependent as occurs in situations such as: (1) the Hamburger effect (a chloride shift when CO_2 is added to venous blood from the tissues); (2) the loss of Donnan equilibrium (a chloride shift from the interstitium to the intravascular compartment to balance the decrease of A_{tot} secondary to capillary leak; and (3) the compensatory response to a primary disturbance in either independent variable. Second, the concept of water dissociation in response to changes in SID is controversial and lacks experimental evidence. In addition, the Stewart approach is not better than the conventional method for understanding acid-base disorders such as hyperchloremic metabolic acidosis secondary to a chloride-rich-fluid load. Finally, several attempts were performed to demonstrate the clinical superiority of the Stewart approach. These studies, however, have severe methodological drawbacks. In contrast, the largest study on this issue indicated the interchangeability of the Stewart and conventional methods. Although the introduction of the Stewart approach was a new insight into acid-base physiology, the method has not significantly improved our ability to understand, diagnose, and treat acid-base alterations in critically ill patients.

Key words: Acid-base metabolism; Stewart approach; Base excess; Bicarbonate; Anion gap; Strong ion difference; Strong ion gap

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In this article, we comprehensively reviewed

the evidence that has been used to argue for the superiority of the Stewart approach over the traditional method for the analysis of acid-base metabolism in critically ill patients. The basic principles of the Stewart approach have severe weaknesses. In addition, the contribution of this method to the understanding of mechanisms is minor; furthermore, from a clinical standpoint, the Stewart approach has no advantage for diagnostic or prognostic purposes compared to the analysis based on bicarbonate, base excess, and albumin-corrected anion gap.

Masevicius FD, Dubin A. Has Stewart approach improved our ability to diagnose acid-base disorders in critically ill patients? *World J Crit Care Med* 2015; 4(1): 62-70 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/62.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.62>

INTRODUCTION

Acid-base disorders are usually found in critically ill patients. Thus, the understanding and identification of these derangements is crucial to the practice of critical-care medicine. Without a doubt, the Stewart approach is an appealing method to analyze acid-base metabolism. The so-called quantitative physicochemical approach has triggered opposing opinions that seem to be related more to passion than to science. The Stewart approach was conceived as a method to revolutionize our ability to understand, predict, and control what happens to hydrogen ions in living systems^[1], whereas the method has instead been characterized as absurd and anachronistic^[2].

The goal of this review is to comprehensively discuss the evidence supporting the conclusion that the Stewart approach, although innovative and attractive, does not significantly contribute to the diagnosis of acid-base abnormalities in critically ill patients.

APPROACHES TO ACID-BASE METABOLISM: THE TRADITIONAL AND THE STEWART APPROACHES

Acid-base disorders can conceivably be described by different methods: First, by a traditional approach, in which the metabolic component of acid-base physiology is based on the analysis of plasma concentrations of bicarbonate (HCO_3^-)^[3]. This basis be further completed with the use of base excess (BE)^[4]. Despite considerable argument over which parameter is better^[5-9], both are usually employed in clinical practice, and all blood-gas analyzers include both calculations. Anion gap (AG) constitutes

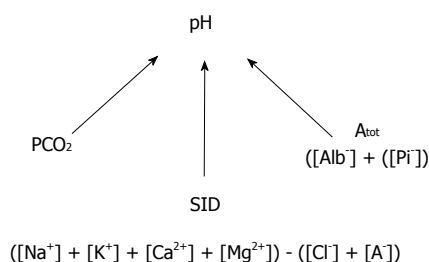


Figure 1 Independent determinants of pH according to the Stewart approach.

an additional diagnostic contribution^[10], though hypoalbuminemia might preclude its usefulness. For this reason, many researchers have recommended to adjust AG to the albumin level ($\text{AG}_{\text{corrected}}$)^[11-16].

An alternative approach is the application of basic physical-chemical principles of aqueous solutions to blood^[1]. Some of the bases of this so-called Stewart approach are: (1) the protons of medium come from dissociation of the water to maintain electroneutrality; (2) the pH is determined by three parameters called "independent variables" because they change primarily and independently of each other (Figure 1). In blood plasma *in vivo* these variables are: (a) the PCO_2 ; (b) the "strong ion difference" (SID), *i.e.*, the difference between the sums of all the strong (fully dissociated, chemically nonreacting) cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) and all the strong anions (Cl^- plus other strong anions such as ketones and lactate); (c) the concentrations of nonvolatile weak acids (A_{tot}), that is, the sum of their dissociated and undissociated forms. Accordingly, neither the pH nor the bicarbonate (dependent variables) can be altered unless one or more of the independent variables change; and (3) The assessment of the metabolic component of acid-base physiology relies on the analysis of plasma SID and A_{tot} .

According to the Stewart approach, metabolic acidosis only occurs if the SID decreases or the A_{tot} increases. On the contrary, metabolic alkalosis develops only if the SID increases or the A_{tot} decreases.

In addition, the Stewart method allows the quantification of the magnitude of each acid-base disorder comparing actual values of the SID and the A_{tot} with normal reference values. Moreover, the approach also allows the computation of the effect of each individual component (Na^+ , K^+ , Ca^{2+} , Mg^{2+} , Cl^- , strong ion gap (SIG), albumin, and phosphate) on the SID and A_{tot} . The Stewart-approach supporters argue that the strength of the method lies in being essentially quantitative because the technique not only measures the magnitude of the deviation of all variables from the normal range but is also mechanistic, as it provides a clear idea of the causes of the acid-base disorders^[1].

DRAWBACKS OF THE PRINCIPLES UNDERLYING THE STEWART APPROACH

Although the Stewart method constitutes an interesting analysis of acid-base metabolism, some of the underlying principles have been questioned: (1) Stewart stated that the protons of the environment come from the dissociation of the water. For example, low SID increases H^+ secondary to water dissociation. This concept, however, is controversial and lacks of experimental evidence; and (2) are the variables SID, PCO_2 and A_{tot} really independent of one another? An independent variable is defined as one that influences the system but is not influenced by the system. The term "system" here, refers to any single aqueous compartment (plasma, the interstitium, the intercellular, or cerebrospinal fluids). Within this scenario, PCO_2 , A_{tot} , and SID fulfill the criteria for independent variables because those parameters directly influence the dissociation reactions that generate weak electrolytes, while they themselves are determined by distinctly separate control mechanisms^[1]. The Stewart analysis, however, involves a single-compartment model and therefore does not take into account exchanges with red blood cells or with the interstitium as occurs when dealing with whole blood; the latter being considered as a tricompartamental model (interstitium, plasma, erythrocytes). In such a setting, PCO_2 , SID and A_{tot} are not completely independent from each other^[17-20], where this lack of independence is exemplified by the following situations: (1) PCO_2 /SID interaction: The Hamburger effect or "chloride shift" is defined as the exchange between Cl^- and HCO_3^- caused by the addition to the venous plasma of CO_2 produced by the cellular metabolism^[17-20]. In this condition, the increase in plasma PCO_2 and HCO_3^- is associated with the entrance of chloride in red blood cells, with the ensuing reduction in the plasma Cl^- . As a consequence of this process, the blood Cl^- becomes lower in the venous than in the arterial blood; (2) A_{tot} /SID: The loss of Donnan equilibrium describes the shift of chloride from the interstitium to the intravascular compartment. This change is produced in order to balance the decrease in A_{tot} secondary to an albumin transudation from the intravascular space in patients with capillary damage and thus an increased permeability^[21]; and (3) the compensatory response to a primary disturbance in either independent variable: In these situations, an adjustment in other variables occurs. For example, hypercapnia causes an increased H^+ , which is compensated by a decrease in Cl^- ^[22] along with an increase in the SID. On the other hand, the compensatory response to reduction in A_{tot} (hypoproteinemia) is a decrease in SID, secondary to an increase in Cl^- ^[23]. The net result of these complementary changes in these theoretically independent variables is an amelioration of the effect

of the primary disorder on H^+ .

In summary, contrary to the principles of Stewart approach, SID, PCO_2 and A_{tot} can be considered not completely independent from each other within certain particular settings (e.g., blood plasma *in vivo*).

UNDERSTANDING THE MECHANISMS OF ACID-BASE ALTERATIONS

A relevant question has to do with an understanding of the mechanisms that underlie the development of hyperchloremic metabolic acidosis after fluid resuscitation with chloride-rich solutions. The traditional approach states that acidosis is caused by a dilution of plasma HCO_3^- ^[24-26]. This classical dilution concept regarding bicarbonate is rejected by the proponents of Stewart's approach, who highlight the mechanistic insight into acid-base physiology as the method's main strength and principal advantage over the traditional model. Therefore, the Stewart approach provides a "strong-ion"-based explanation for the mechanism of dilutional acidosis. They argue that dilutional acidosis is explained by a decrease in the SID^[1,27-31].

This issue has been comprehensively studied by other researchers^[32,33]. Based on simulations of dilution studies along with *in vitro* experiments, they tried to clarify the chemical mechanism responsible for dilutional acidosis. Consequently, they examined the effects of diluting normal extracellular fluid with different solutions both in a closed system (*i.e.*, a system not exchanging matter with the environment, such as venous blood before reaching the lung) and in a system open to gases (*i.e.*, one capable of equilibrating with the PCO_2). They observed that dilution of extracellular fluid did not lead to any detectable change in the H^+ when the system was closed. The explanation was that all the determinants of the H^+ , SID, PCO_2 and A_{tot} were equally diluted so that their relative proportions did not change. In actuality, the decrease in the SID (leading to acidosis) was exactly balanced by the decrease in the CO_2 content and noncarbonic buffers (leading to alkalosis). As a consequence, the pH did not change. On the contrary, acidosis was only found when the system was open to the gases with normal PCO_2 (40 mmHg). In this situation, the CO_2 entered into the system because of the differing tensions between the gas phase and the diluted solution until the PCO_2 was equilibrated. Therefore, the excess of protons observed in this dilutional acidosis came from CO_2 hydration to carbonic acid (Figure 2). In other words, the chemical mechanism of the dilutional acidosis in blood plasma involves the dilution of an open CO_2/HCO_3^- buffer system, where the buffer base (*i.e.*, the HCO_3^-) is diluted but not the buffer acid (the CO_2).

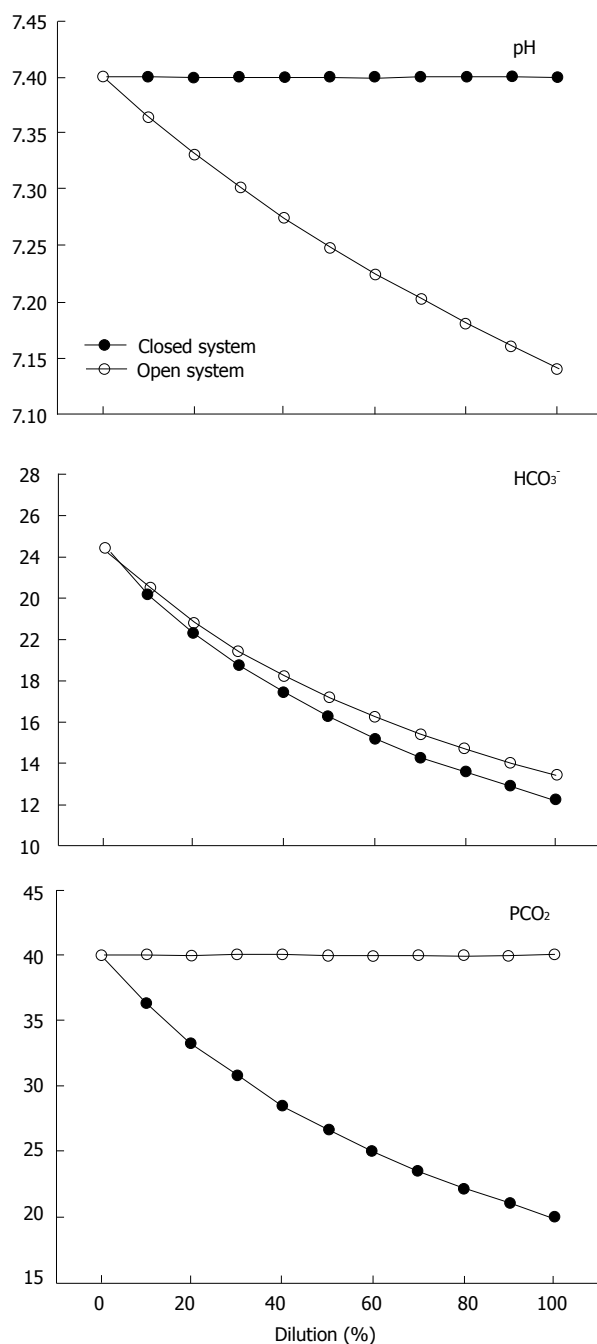


Figure 2 Behavior of pH (top), HCO_3^- (middle) and PCO_2 (bottom) in a closed system (black dots) and in an open system with a PCO_2 of 40 mmHg (with dots), during stepwise dilution with 0.9% NaCl, as modified from Gattinoni *et al.*^[32].

Stated in brief, the Stewart and the traditional approaches may account for these results^[32,33]: (1) according to Stewart's approach, since the SID and the A_{tot} remain unchanged after opening the system to gases, the only determinant of the decrease in the pH is the increase in PCO_2 or, more precisely, the increase in CO_2 content. Therefore, the change in the SID - it being merely a mathematical construct - is not the cause of dilutional acidosis, but rather a marker for the dilutional process. In addition, the increase in water dissociation is not the chemical

mechanism of dilutional acidosis, and consequently the Stewart approach does not provide any mechanistic insight into acid-base disorders^[33]; and (2) according to the traditional model, the acidosis is explained by the increase in the PCO_2 in the face of a dilution of the buffer's base.

CLINICAL USEFULNESS OF THE STEWART APPROACH IN CRITICALLY ILL PATIENTS

Although the principles of the Stewart approach have weaknesses and this method does not offer clear advantages for explaining mechanisms, several attempts have been made to show the superiority of that approach over conventional analysis in the diagnosis of acid-base alterations in critically ill patients.

The first question is if the SID is really different from the buffer base concentration (BB). The SID is actually equal to the buffer base described more than half a century ago. Consequently, the BE becomes the deviation of SID from its normal value. The SID and the BB are mirror images of each other^[34].

Nevertheless, Fencel *et al.*^[35] studied a series of 152 critically ill patients and concluded that the Stewart approach allowed a detection and quantification of all the various individual components of even the most complex acid-base disturbances seen in critically ill patients^[35]. In that study, the Stewart approach was able to detect metabolic acidosis in 20 patients with normal HCO_3^- and in 22 patients with normal BE. Low SID was unnoticed by changes in BE, because the low SID acidosis was masked by the alkalinizing effect of hypoalbuminemia. The $\text{AG}_{\text{corrected}}$, however, adequately identified all patients with elevated unmeasured anions. For this reason, a correct use of the traditional approach would have allowed a similar diagnosis. In addition, in normal volunteers, the SIG, the variable from the Stewart approach that quantifies unmeasured anions, was 8 mEq/L, which is an extremely high value. The expected values should have been close to zero. This finding suggests the presence of some methodological error.

In another study, Boniatti *et al.*^[36] concluded that their main result was the demonstration of a greater sensitivity on the part of physicochemical evaluation in identifying acid-base disorders in critically ill patients^[36]. An evaluation according to the Stewart method allowed an additional diagnosis of a metabolic disorder in 34% of the cases, because of the greater sensitivity of the SID compared to BE. These results, however, might have been expected because of the methodological limitations of the study. The authors considered as normal BE values from -5 to 5 mmol/L, while the normal SID was arbitrarily defined as values from

Table 1 Examples of acid-base disorders

	Patient 1	Patient 2
Measured variables		
Sodium (mmol/L)	151	146
Potassium (mmol/L)	3.4	3.8
Calcium (mg/dL)	7.0	7.2
Magnesium (mmol/L)	2.0	1.8
Phosphate (mmol/L)	1.0	2.0
Albumin (g/L)	27.0	27.0
Chloride (mmol/L)	121	124
pH	7.48	7.43
PaCO ₂ (mmHg)	29.0	30.2
Lactate (mmol/L)	2.0	1.3
Derived variables		
HCO ₃ ⁻ (mmol/L)	21.5	20
BE (mmol/L)	-0.7	-3.8
AG (mmol/L)	12.4	6.3
SID (mmol/L)	29.9	28.8
SIG (mmol/L)	4.5	-1.4

BE: Base excess; AG: Anion gap; SID: Strong ion difference; SIG: Strong ion gap. Modified from Boniatti *et al*^[36].

38 to 42 mmol/L. Consequently, the diagnosis of metabolic acidosis required a decrease in the BB of 5 mmol/L, when the BE was used as the criterion. In contrast, a reduction of only 2 mmol/L in BB identified the presence of metabolic acidosis when the SID was used. Therefore, the use of a more sensitive threshold for the diagnosis of metabolic acidosis by means of SID completely explained the results. This study has several other limitations - such as not measuring the arterial blood gases and electrolytes simultaneously, the negative values of SIG that were frequently found, the arbitrary choice of normal ranges, and the failure to evaluate the agreement between the acid-base variables of both approaches. Finally, the authors presented two cases to illustrate the diagnosis of metabolic acidosis by means of the Stewart approach (Table 1), but unfortunately those two were misinterpreted. Actually, the authors mistakenly chose patients with respiratory alkalosis instead of metabolic acidosis. The presence of the low SID was the result of the renal compensation for a respiratory alkalosis, which condition was the primary diagnosis of their cases, as indicated by the high pH and low PCO₂ values. As previously shown, the use of the Stewart approach, without consideration of the metabolic response to a primary respiratory disorder can lead to an incorrect diagnosis in 15% of the cases^[37]. Indeed, the examples cited here adequately and definitively illustrate the very drawbacks of the Stewart approach, instead of its advantages.

Kaplan *et al*^[38] performed a controlled study to show that the clinical use of the Stewart approach improved the accuracy of acid-base diagnosis and reduced the possibility of an inappropriate fluid loading. For this purpose, one-hundred consecutive trauma patients admitted to a surgical ICU were prospectively allocated to care by either one phy-

sician who was to use the Stewart approach or four other practitioners who would employ the conventional method. The diagnoses and interventions made by the "conventional physicians" were reviewed by the "Stewart physician". The results showed that the conventional approach missed a lot of diagnoses. Moreover, the acid-base balance normalized sooner (3.3 ± 3.4 d vs 8.3 ± 7.4 d) and fewer volume expansions were given through the use of Stewart approach. The ostensible conclusion was that the physician who used the Stewart approach more correctly diagnosed and treated the patients compared to the other four physicians who only utilized the conventional method. Nevertheless, the criteria used by these physicians were not presented in the study, and the Stewart physician himself determined what was right or wrong without any established definition. For example, 43 of the 50 patients treated by the physicians who used the traditional analysis were unnecessarily volume-expanded because of the presence of hyperchloremic metabolic acidosis. The Stewart approach, however, would not have been needed for that diagnosis. Consequently, the absence of a well-defined methodology precludes any conclusion from this trial.

Some studies have assessed SIG as a potential tool, not only for the measurement of anions but also as a surrogate of tissue hypoperfusion and a predictor of outcome. A theoretical advantage of SIG over AG is that the parameter remains stable and reliable, even in cases of extreme variations in the PCO₂ and pH^[39].

Kaplan *et al*^[40] studied the acid-base determinants of the outcome in trauma patients with major vascular injuries and concluded that SIG was a better predictor of mortality than AG^[40]. Regrettably, these conclusions were not supported by the findings. The area under the ROC curve and the confidence intervals for SIG, BE and AG were quite similar. Therefore, these acid-base variables showed the same prognostic ability.

Other studies performed in pediatric critically ill patients came to similar conclusions^[41,42]. The SIG was more strongly associated with mortality than traditional variables such as BE, AG, or lactate levels. Nevertheless, a proper evaluation of the unmeasured anions by the traditional method was not performed because the AG values were not corrected with respect to albumin levels.

A study by Funk *et al*^[43] investigated the association between the SIG and the long-term outcome after cardiac arrest, in patients treated with therapeutic hypothermia^[43]. The authors concluded that the SIG, measured 12 h after the return of spontaneous circulation, was an independent predictor of outcome. The AG and the SIG were strongly correlated, but the predictive capacity of the AG was not tested. Surprisingly, an editorial entitled

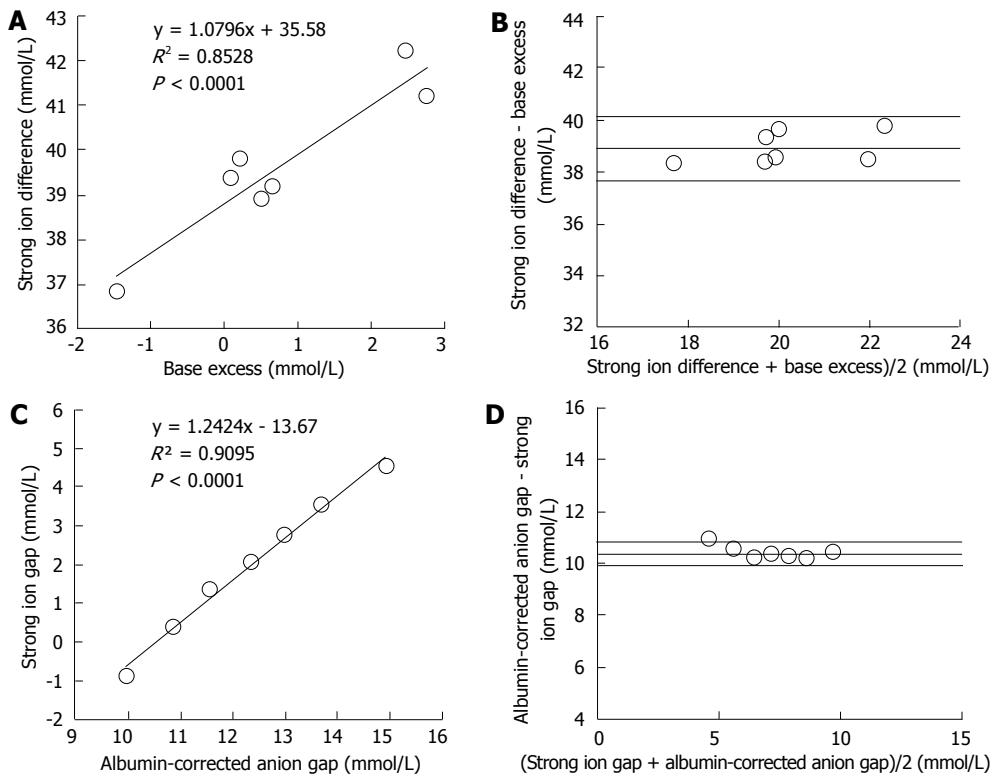


Figure 3 Regression and Bland and Altman analysis between metabolic parameters of different approaches in seven normal volunteers. A: Lineal regression between base excess and strong ion difference; B: Agreement between base excess and strong ion difference; C: Lineal regression between albumin-corrected anion gap and strong ion gap; D: Agreement between albumin-corrected anion gap and strong ion gap. Panel B and D display the relationship between the mean value and the difference of both measurements. The lines indicate the mean difference between both parameters (bias) \pm 2 SD (95% limits of agreement). Modified from Dubin *et al*^[37].

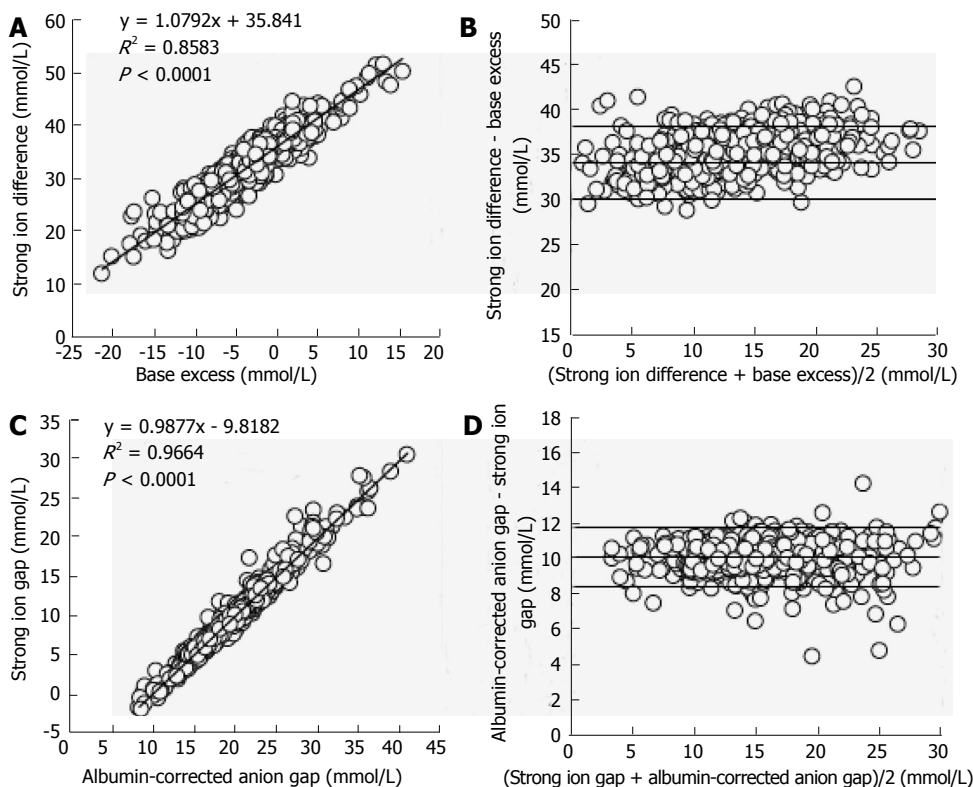


Figure 4 Regression and Bland and Altman analysis between metabolic parameters of different approaches in 935 critically ill patients. A: Lineal regression between base excess and strong ion difference; B: Agreement between base excess and strong ion difference; C: Lineal regression between albumin-corrected anion gap and strong ion gap; D: Agreement between albumin-corrected anion gap and strong ion gap. Panel B and D display the relationship between the mean value and the difference between both measurements. The lines indicate the mean difference between both parameters (bias) \pm 2 SD (95% limits of agreement). Modified from Dubin *et al*^[37].

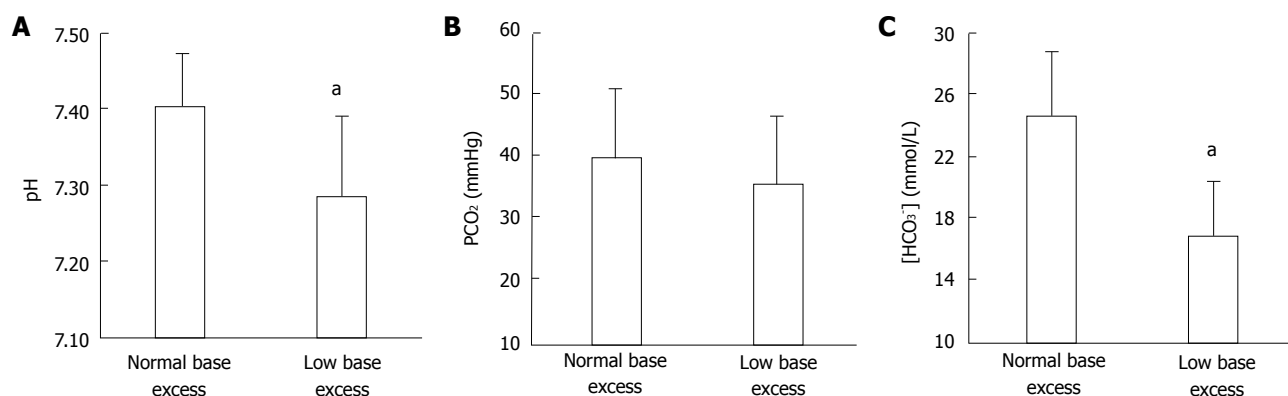


Figure 5 Arterial pH, and bicarbonate levels in patients with severe hyperlactatemia. Values for (A) arterial pH, (B) PCO₂, and (C) bicarbonate ([HCO₃⁻]) in patients with severe hyperlactatemia, with normal or low base excess. ^a*P* < 0.05 vs the other group.

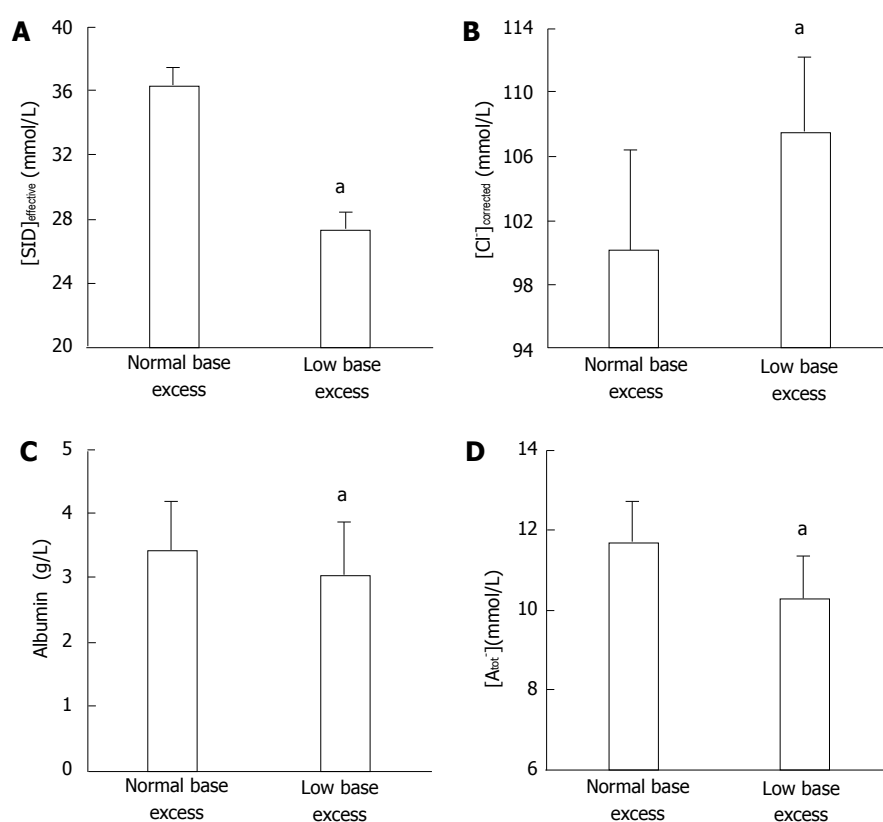


Figure 6 Strong-ion difference, sodium-corrected chloride, albumin, and nonvolatile weak acid levels in severe hyperlactatemia patients. Values for (A) the effective strong-ion difference (SID_{effective}), (B) sodium-corrected chloride levels (Cl⁻_{corrected}), (C) the albumin concentration, and (D) nonvolatile weak acid (A_{tot}) levels in patients with severe hyperlactatemia, with normal or low base excess. ^a*P* < 0.05 vs the other group. SID_{effective}: Effective strong-ion difference.

"Another Nail in the Coffin of Traditional Acid-base Quantification" was published along with this same study^[44].

We compared the traditional and Stewart approaches in a series of 935 critically ill patients and in 7 healthy volunteers in order to demonstrate that the Stewart approach does not offer any diagnostic or prognostic advantage^[37]. With the use of an analysis based on HCO₃⁻, BE and AG_{corrected}, only 1% of the patients with low SID acidosis were left undiagnosed. In contrast, diagnosis by the Stewart approach was normal in 2% of the patients in whom

metabolic acidosis was identified by the criteria of decreased HCO₃⁻ and BE, and increased AG_{corrected}. Moreover, in normal volunteers, BE and SID, and AG_{corrected} and SIG were strongly correlated, exhibiting narrow limits of agreement (Figure 3). Something similar occurred in the critically ill patients (Figure 4). In addition, the prognostic ability of the different acid-base parameters was similar. The results from this study suggest that the approaches are rather similar in terms of diagnostic and prognostic performance.

Another relevant issue with the Stewart approach

is the poor reproducibility with respect to the determination of its variables. A study analyzed 179 routine blood samples from consecutive patients over a 3-mo period. The determinations were performed by two automated blood-chemistry analyzers. An analysis of the agreement obtained indicated a lack of reproducibility among the simultaneous measurements as illustrated by the wide 95% limits of agreement: 10 mmol/L for SID and 12 mmol/L for SIG^[45].

Finally, we demonstrated a similar diagnostic performance for the two approaches in a complex metabolic disorder^[46]. Of the patients admitted to the ICU with severe hyperlactatemia (lactate levels ≥ 4 mmol/L), some 20% had normal pH, HCO_3^- , and BE - but also normal SID. This finding was explained by the simultaneous presence of hypochloremic metabolic alkalosis. Equimolar changes had occurred in the variables of the two approaches that had allowed the identification of the mixed metabolic alteration. The Stewart approach showed normal SID values together with a low chloride level, while the traditional analysis indicated an increase in the difference between the changes in AG and HCO_3^- (Figures 5 and 6). Consequently, the Stewart and conventional approaches were able to describe this complex acid-base disorder in a similar way.

CONCLUSION

The Stewart approach has allowed a new insight into acid-base physiology. Unfortunately, the introduction of that method did not result in relevant advantages, compared to the judicious use of HCO_3^- , BE, and AG^{corrected} either for an understanding of the mechanisms of acid-base alterations or for diagnosis or prognosis. Furthermore, the Stewart approach is cumbersome, requires more determinations and calculations, and is more time-consuming and expensive. On the basis of the compelling evidence that we have discussed here, in order to improve acid-base evaluation we only need to continue with the proper use of the old tools.

REFERENCES

- 1 Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983; **61**: 1444-1461 [PMID: 6423247 DOI: 10.1139/y83-207]
- 2 Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. *Acta Anaesthesiol Scand Suppl* 1995; **107**: 123-128 [PMID: 8599264 DOI: 10.1111/j.1399-6576.1995.tb04346.x]
- 3 Narins RG. (Editor). Maxwell and Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism. 5th ed. New York: McGraw-Hill, 1994
- 4 Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine* (Baltimore) 1980; **59**: 161-187 [DOI: 10.1097/00005792-198005000-00001]
- 5 Siggaard-Andersen O. The Acid-Base Status of the Blood. 4th ed. Baltimore: Williams & Wilkins, 1974
- 6 Schwartz WB, Relman AS. A critique of the parameters used in the evaluation of acid-base disorders. "Whole-blood buffer base" and "standard bicarbonate" compared with blood pH and plasma bicarbonate concentration. *N Engl J Med* 1963; **268**: 1382-1388 [PMID: 13987401 DOI: 10.1056/NEJM196306202682503]
- 7 Bunker JP. The great trans-atlantic acid-base debate. *Anesthesiology* 1965; **26**: 591-594 [PMID: 14338914]
- 8 Severinghaus JW. Acid-base balance nomogram--a Boston-Copenhagen detente. *Anesthesiology* 1976; **45**: 539-541 [PMID: 973708 DOI: 10.1097/0000542-197611000-00013]
- 9 Severinghaus JW. Siggaard-Andersen and the "Great Trans-Atlantic Acid-Base Debate". *Scand J Clin Lab Invest Suppl* 1993; **214**: 99-104 [PMID: 8332859 DOI: 10.3109/00365519309090685]
- 10 Emmet M, Narins RG. Clinical use of anion gap. *Medicine* (Baltimore) 1977; **56**: 38-54 [DOI: 10.1097/00005792-197756010-00002]
- 11 Figge J, Jabor A, Kazda A, Fencel V. Anion gap and hypoalbuminemia. *Crit Care Med* 1998; **26**: 1807-1810 [PMID: 9824071 DOI: 10.1097/0003246-199811000-00019]
- 12 Durward A, Mayer A, Skellett S, Taylor D, Hanna S, Tibby SM, Murdoch IA. Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap. *Arch Dis Child* 2003; **88**: 419-422 [PMID: 12716714 DOI: 10.1136/adc.88.5.419]
- 13 Hatherill M, Waggie Z, Purves L, Reynolds L, Argent A. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. *Arch Dis Child* 2002; **87**: 526-529 [PMID: 12456555 DOI: 10.1136/adc.87.6.526]
- 14 Carvounis CP, Feinfeld DA. A simple estimate of the effect of the serum albumin level on the anion Gap. *Am J Nephrol* 2000; **20**: 369-372 [PMID: 11092993 DOI: 10.1159/000013618]
- 15 Taylor D, Durward A, Tibby SM, Thorburn K, Holton F, Johnstone IC, Murdoch IA. The influence of hyperchloraemia on acid base interpretation in diabetic ketoacidosis. *Intensive Care Med* 2006; **32**: 295-301 [PMID: 16447033 DOI: 10.1007/s00134-005-0009-1]
- 16 Corey HE. The anion gap (AG): studies in the nephrotic syndrome and diabetic ketoacidosis (DKA). *J Lab Clin Med* 2006; **147**: 121-125 [PMID: 16503241 DOI: 10.1016/j.lab.2005.10.004]
- 17 Hamburger HJ. Anionenwanderungen in Serum und Blut unter dem Einfluss von CO₂, Saeure und Alkali. *Biochem Z* 1918; **86**: 309-324
- 18 Westen EA, Prange HD. A reexamination of the mechanisms underlying the arteriovenous chloride shift. *Physiol Biochem Zool* 2003; **76**: 603-614 [PMID: 14671708 DOI: 10.1086/380208]
- 19 Langer T, Zani L, Carlesso E, Protti A, Caironi P, Chierichetti M, Caspani ML, Gattinoni L. Contribution of red blood cells to the compensation for hypocapnic alkalosis through plasmatic strong ion difference variations. *Critical Care* 2011; **15** (Suppl 1): P134 [DOI: 10.1186/cc9554]
- 20 Langer T, Carlesso E, Gattinoni L. The Hamburger Effect: Beyond Chloride Shift. *Am J Respir Crit Care Med* 2012; **185**: A3168 [DOI: 10.1164/ajrccm.conference.2012.185.1_MeetingAbstracts.A3168]
- 21 Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock* 1998; **9**: 364-368 [PMID: 9617887 DOI: 10.1097/00024382-199805000-00009]
- 22 Polak A, Haynie GD, Hays RM, Schwartz WB. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. I. Adaptation. *J Clin Invest* 1961; **40**: 1223-1237 [PMID: 13736670 DOI: 10.1172/JCI104353]
- 23 Wilkes P. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. *J Appl Physiol* (1985) 1998; **84**: 1740-1748 [PMID: 9572825]
- 24 Shires GT, Holman J. Dilution acidosis. *Ann Intern Med* 1948; **28**: 557-559 [PMID: 18905223 DOI: 10.7326/0003-4819-28-3-557]
- 25 Asano S, Kato E, Yamauchi M, Ozawa Y, Iwasa M. The mechanism of acidosis caused by infusion of saline solution. *Lancet* 1966; **1**: 1245-1246 [PMID: 4161214 DOI: 10.1016/S0140-6736(66)90248-0]
- 26 Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. *Kidney Int* 1975; **8**: 279-283 [PMID: 536 DOI: 10.1038/ki.1975.114]

- 27 **Kellum JA**. Saline-induced hyperchloremic metabolic acidosis. *Crit Care Med* 2002; **30**: 259-261 [PMID: 11902280 DOI: 10.1097/00003246-200201000-00046]
- 28 **Constable PD**. Hyperchloremic acidosis: the classic example of strong ion acidosis. *Anesth Analg* 2003; **96**: 919-922 [PMID: 12651634 DOI: 10.1213/01.ANE.0000053256.77500.9D]
- 29 **Mathes DD**, Morell RC, Rohr MS. Dilutional acidosis: is it a real clinical entity? *Anesthesiology* 1997; **86**: 501-503 [PMID: 9054271 DOI: 10.1097/00000542-199702000-00028]
- 30 **Prough DS**, White RT. Acidosis associated with perioperative saline administration: dilution or delusion? *Anesthesiology* 2000; **93**: 1167-1169 [PMID: 11046200 DOI: 10.1097/00000542-20001100-00005]
- 31 **Prough DS**, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. *Anesthesiology* 1999; **90**: 1247-1249 [PMID: 10319767 DOI: 10.1097/00000542-199905000-00003]
- 32 **Gattinoni L**, Carlesso E, Maiocchi G, Polli F, Cadringer P. Dilutional acidosis: where do the protons come from? *Intensive Care Med* 2009; **35**: 2033-2043 [PMID: 19763537 DOI: 10.1007/s00134-009-1653-7]
- 33 **Doberer D**, Funk GC, Kirchner K, Schneeweiss B. A critique of Stewart's approach: the chemical mechanism of dilutional acidosis. *Intensive Care Med* 2009; **35**: 2173-2180 [PMID: 19533091 DOI: 10.1007/s00134-009-1528-y]
- 34 **Kellum JA**. Determinants of blood pH in health and disease. *Crit Care* 2000; **4**: 6-14 [PMID: 11094491 DOI: 10.1186/cc644]
- 35 **Fencl V**, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Care Med* 2000; **162**: 2246-2251 [PMID: 11112147 DOI: 10.1164/ajrccm.162.6.9904099]
- 36 **Boniatti MM**, Cardoso PR, Castilho RK, Vieira SR. Acid-base disorders evaluation in critically ill patients: we can improve our diagnostic ability. *Intensive Care Med* 2009; **35**: 1377-1382 [PMID: 19367388 DOI: 10.1007/s00134-009-1496-2]
- 37 **Dubin A**, Meneses MM, Masevicius FD, Moseinco MC, Kutscherauer DO, Ventrice E, Laffaire E, Estenssoro E. Comparison of three different methods of evaluation of metabolic acid-base disorders. *Crit Care Med* 2007; **35**: 1264-1270 [PMID: 17334252 DOI: 10.1097/01.CCM.0000259536.11943.90]
- 38 **Kaplan LJ**, Cheung NH, Maerz L, Lui F, Schuster K, Luckianow G, Davis K. A physicochemical approach to acid-base balance in critically ill trauma patients minimizes errors and reduces inappropriate plasma volume expansion. *J Trauma* 2009; **66**: 1045-1051 [PMID: 19359913 DOI: 10.1097/TA.0b013e31819a04be]
- 39 **Morgan TJ**, Cowley DM, Weier SL, Venkatesh B. Stability of the strong ion gap versus the anion gap over extremes of PCO₂ and pH. *Anaesth Intensive Care* 2007; **35**: 370-373 [PMID: 17591130]
- 40 **Kaplan LJ**, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med* 2004; **32**: 1120-1124 [PMID: 15190960 DOI: 10.1097/01.CCM.0000125517.28517.74]
- 41 **Durward A**, Tibby SM, Skellett S, Austin C, Anderson D, Murdoch IA. The strong ion gap predicts mortality in children following cardiopulmonary bypass surgery. *Pediatr Crit Care Med* 2005; **6**: 281-285 [PMID: 15857525 DOI: 10.1097/00130478-200505000-00038]
- 42 **Balasubramanyan N**, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med* 1999; **27**: 1577-1581 [PMID: 10470767 DOI: 10.1097/00003246-199908000-00030]
- 43 **Funk GC**, Doberer D, Sterz F, Richling N, Kneidinger N, Lindner G, Schneeweiss B, Eisenburger P. The strong ion gap and outcome after cardiac arrest in patients treated with therapeutic hypothermia: a retrospective study. *Intensive Care Med* 2009; **35**: 232-239 [PMID: 18853143 DOI: 10.1007/s00134-008-1315-1]
- 44 **Honore PM**, Joannes-Boyau O, Boer W. Strong ion gap and outcome after cardiac arrest: another nail in the coffin of traditional acid-base quantification. *Intensive Care Med* 2009; **35**: 189-191 [PMID: 18853142 DOI: 10.1007/s00134-008-1316-0]
- 45 **Nguyen BV**, Vincent JL, Hamm JB, Abalain JH, Carre JL, Nowak E, Ahmed MO, Arvieux CC, Gueret G. The reproducibility of Stewart parameters for acid-base diagnosis using two central laboratory analyzers. *Anesth Analg* 2009; **109**: 1517-1523 [PMID: 19713255 DOI: 10.1213/ANE.0b013e3181b62664]
- 46 **Tuhay G**, Pein MC, Masevicius FD, Kutscherauer DO, Dubin A. Severe hyperlactatemia with normal base excess: a quantitative analysis using conventional and Stewart approaches. *Crit Care* 2008; **12**: R66 [PMID: 18466618 DOI: 10.1186/cc6896]

P- Reviewer: Abdel-Salam OME, Jeschke MG, Saniabadi AR

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Observational Study

Serum bicarbonate may independently predict acute kidney injury in critically ill patients: An observational study

Anuksha Gujadhur, Ravindranath Tiruvoipati, Elizabeth Cole, Saada Malouf, Erum Sahid Ansari, Kim Wong

Anuksha Gujadhur, Kim Wong, Department of Renal Medicine, Frankston Hospital, Frankston VIC 3199, Australia

Ravindranath Tiruvoipati, School of Public Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Victoria 3800, Australia

Ravindranath Tiruvoipati, Elizabeth Cole, Saada Malouf, Erum Sahid Ansari, Department of Intensive Care Medicine, Frankston Hospital, Frankston VIC 3199, Australia

Author contributions: Gujadhur A, Cole E, Malouf S, Ansari ES and Wong K contributed to conception and design, acquisition of data, interpretation of data, drafting the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published; Tiruvoipati R contributed to conception and design, acquisition of data, or analysis and interpretation of data; Tiruvoipati R had been involved in drafting the manuscript or revising it critically for important intellectual content; Tiruvoipati R had given final approval of the version to be published; all authors read and approved the final manuscript. **Ethics approval:** Human Ethics Review Committee of Peninsula Health have reviewed (Ref HREC/11/PH/63) and approved the study for publication. a copy of approval can be provided on request.

Informed consent: The Human Ethics Review Committee of Peninsula Health consent from individual patients as the study was seen as a retrospective audit of data routinely collected for patient care and not experimental research.

Conflict-of-interest: None of the authors have commercial association or financial involvement that might pose a conflict of interest in connection with this article.

Data sharing: Data presented in the manuscript is anonymised and the risk of identifying individual patient is very low. No additional data is available other than stated in the manuscript for this study.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Ravindranath Tiruvoipati, Department of Intensive Care Medicine, Frankston Hospital, 2 Hastings Road Frankston, Victoria 3199,

Australia. travindranath@hotmail.com

Telephone: +61-431-279347

Fax: +61-3978-47398

Received: May 10, 2014

Peer-review started: May 10, 2014

First decision: June 6, 2014

Revised: December 27, 2014

Accepted: January 9, 2015

Article in press: January 12, 2015

Published online: February 4, 2015

Abstract

AIM: To explore whether serum bicarbonate at admission to intensive care unit (ICU) predicted development of acute kidney injury (AKI).

METHODS: We studied all patients admitted to our ICU over a 2 year period (February 2010 to 2012). The ICU has a case mix of medical and surgical patients excluding cardiac surgical, trauma and neurosurgical patients. We analysed 2035 consecutive patients admitted to ICU during the study period. Data were collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Ambiguous data were checked for accuracy where indicated. AKI was defined using the Kidney Disease Improving Global Outcomes criteria. Patients were divided into two groups; patients who developed AKI or those who did not, in order to compare the baseline characteristics, and laboratory and physiologic data of the two cohorts. Regression analysis was used to identify if serum bicarbonate on admission predicted the development of AKI.

RESULTS: Of 2036 patients 152 (7.5%) were excluded due to missing data. AKI developed in 43.1% of the patients. The AKI group, compared to the non-AKI group, was sicker based on their lower systolic, diastolic and mean arterial pressures and a higher acute

physiology and chronic health evaluation (APACHE) III and SAPS II scores. Moreover, patients who developed AKI had more co-morbidities and a higher proportion of patients who developed AKI required mechanical ventilation. The multi-regression analysis of independent variables showed that serum bicarbonate on admission (OR = 0.821; 95%CI: 0.796-0.846; $P < 0.0001$), APACHE III (OR = 1.011; 95%CI: 1.007-1.015; $P < 0.0001$), age (OR = 1.016; 95%CI: 1.008-1.024; $P < 0.0001$) and presence of sepsis at ICU admission (OR = 2.819; 95%CI: 2.122-23.744; $P = 0.004$) were each significant independent predictors of AKI. The area under the ROC curve was 0.8 (95%CI: 0.78-0.83), thereby demonstrating that the predictive model has relatively good discriminating power for predicting AKI.

CONCLUSION: Serum bicarbonate on admission may independently be used to make a diagnosis of AKI.

Key words: Acute kidney injury; Bicarbonate; Mortality; Sepsis

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Metabolic acidosis is often associated with acute kidney injury (AKI) and can result in multiple complications, including cardiac dysfunction, hypotension and mortality. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an intensive care unit (ICU) setting. We demonstrated that serum bicarbonate on admission may independently be used to make a diagnosis of AKI, in a mixed ICU setting. Our results are relevant since serum bicarbonate is inexpensive and easily available, which will enable initiate prompt treatment of AKI, for better outcomes.

Gujadhur A, Tiruvoipati R, Cole E, Malouf S, Ansari ES, Wong K. Serum bicarbonate may independently predict acute kidney injury in critically ill patients: An observational study. *World J Crit Care Med* 2015; 4(1): 71-76 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/71.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.71>

INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decline in renal function, resulting in the inability to excrete metabolic wastes and maintain proper fluid, electrolyte and acid base balance. It results in multiple complications including hyperkalaemia, acidosis, volume overload, encephalopathy and anaemia^[1]. Patients who develop AKI have worse long-term outcomes, especially in the immediate post-intensive care unit (ICU) period^[2].

Metabolic acidosis, which is often associated with

AKI, can result in cardiac dysfunction, hypotension, increased risk of infection and mortality. Hence clinical practice guidelines recommend initiation of alkali therapy when serum bicarbonate level is ≤ 22 mmol/L^[1] although a recent Cochrane review demonstrated the benefit of sodium bicarbonate in AKI management as equivocal^[3].

A more thorough understanding of the impact and association of different risk factors with AKI is very important for designing predictive models of patients at high risk of developing this lethal condition, in order that preventative strategies may be created to benefit such a group. Predictive models for development of AKI already exist in cardiac-surgery critically ill patients^[4-6]. There is however a lack of meaningful predictive models in mixed and medical ICUs. Most of the prediction models in these context have focused on the impact on mortality of AKI in ICU patients^[7,8].

Multiple biomarkers including serum and urinary CysC, neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) have been used to predict AKI^[9]. The usefulness of these serum biomarkers in predicting the development of AKI appears to be evolving. Yet assay to assays to identify these biomarkers are expensive and not widely available.

There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an ICU setting. Measurement of serum bicarbonate is possible in most hospital settings and is not expensive. Hence we aimed to primarily assess the role of serum bicarbonate, measured during the first 24 h of ICU admission, in diagnosing AKI and identify other independent predictors of AKI.

MATERIALS AND METHODS

Ethics

The Human Research Ethics Committee of Peninsula Health reviewed the study protocol and waived the requirement for full ethics committee application, as the study was seen as a retrospective audit of data routinely collected for patient care and not experimental research.

Study design and setting

We studied all patients admitted to our ICU over a 2 year period (February 2010 to 2012). The ICU has a case mix of medical and surgical patients excluding cardiac surgical, trauma and neurosurgical patients. The study was undertaken at Frankston Hospital, the acute care hospital for Peninsula Health. The hospital is a tertiary referral centre that is affiliated with Monash University.

Clinical and laboratory features at admission and during ICU stay were collected from our ICU database (called STATIC), our hospital's pathology

Table 1 Comparison of demographical and clinical characteristics at the time of admission to intensive care

	NO AKI (n = 1006)	AKI (n = 877)	P value
Age (yr)	61.4 (18.8)	66.2 (16.6)	< 0.0001
Sex, M:F	1.1:1 (726:662)	1.1:1 (242:220)	0.978
Requirement for mechanical ventilation	46%	51.5%	0.01
Severity of illness			
APACHE III	47.8 (25.3)	63 (35.7)	< 0.0001
SAPS II	33.7 (13.8)	45.9 (17.6)	< 0.0001
Vital signs			
Heart rate (/min)	99 (22)	105 (23)	< 0.001
Respiratory rate (/min)	24 (6.6)	26 (7.5)	< 0.001
Temperature ¹ (°C)	35.3 (0.9)	35.2 (1.2)	0.004
Systolic BP ¹ (mmHg)	102.9 (16.8)	96.5 (16.9)	< 0.001
Diastolic BP ¹ (mmHg)	55.8 (12.2)	52.3 (12.7)	< 0.001
MAP (mmHg)	71.3 (12.7)	67.0 (12.8)	< 0.001

¹Lowest. Data are presented in mean \pm SD; number of patients where data were available for analyses. SAPS II: Simplified acute physiology score II; APACHE III: Acute physiology age and chronic health evaluation III; BP: Blood pressure; MAP: Mean arterial pressure.

database and the case records of the patients included in the study. Data were collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Ambiguous data were checked for accuracy where indicated.

Definition of parameters

Clinical and laboratory features at admission and during ICU stay were studied. AKI was defined using the Kidney Disease Improving Global Outcomes (KDIGO) Practice Guidelines^[10]. As per the guidelines, a patient was considered to have AKI if there was an increase in serum creatinine by 26.5 μ mol/L or more within 48 h, or an increase in serum creatinine to 1.5 times baseline or more within the last 7 d. Baseline renal function was defined as the lowest known serum creatinine during the preceding 3 mo prior to hospital admission. Patients with unknown baseline serum creatinine were excluded from the study. Patients were considered as having new AKI if they did not have AKI on ICU admission but subsequently met the KDIGO Guidelines during the first 48 h of ICU presentation. Metabolic acidosis was defined as pH < 7.35 and an arterial bicarbonate < 20 mmol/L.

Patient population and data collection

The patients were divided into two groups, the AKI and non-AKI groups, in order to investigate if there were differences in relation to all the studied parameters. Thereafter, the proportion of patients with metabolic acidosis in the AKI group was determined. The presence of hypertension, diabetes and peripheral vascular disease, as well as the length of ICU and hospital stays were analysed in all patients included in the study. The acute physiology and chronic health evaluation (APACHE) III score^[11] and simplified acute

physiology score (SAPS) II^[12] were calculated for the first 24 h of admission. Physiological parameters during the first 24 h of ICU admission, including vital signs and partial pressures of oxygen and carbon dioxide were recorded. Serum urea and creatinine were recorded during the first 48 h of ICU admission, at 24 h-intervals, in all patients included in the study. The laboratory parameters consisted of serum bicarbonate, pH, lactate, albumin, urea, potassium, white cell count (WCC) and glucose levels.

Statistical analysis

Statistical analysis was performed by a biomedical statistician. Categorical data were assessed using Fisher's exact test. Student's *t* tests (for parametric data) or Mann-Whitney *U* (Non parametric) tests was used for continuously-scaled data.

Logistic regression analysis was used to distinguish independent predictors of hospital mortality. In regression analysis models data variables were entered using "Enter" method. The first model contained data variables including age, mean BP, serum lactate, pH, APACHE III score, serum bicarbonate on admission, presence of sepsis at admission and the need for mechanical ventilation. Further models were constructed aiming for a parsimonious model. Every model constructed was assessed by Cox and Snell and Nagelkerke R square and Hosmer-Lemeshow goodness-of-fit statistic. Regression models were constructed using Wald statistic. The final model contained four variables including age, sepsis on admission, serum bicarbonate and APACHE III score. A *P* value < 0.05 was considered to be statistical significant. Data analyses were performed using IBM SPSS statistics version 22.0 (SPSS Inc, Chicago, IL).

RESULTS

Over the two year study period 2035 patients were admitted to our ICU. We excluded 152 (7.5%) patients due to missing data on serum creatinine. 877 patients (43.1%) of the cohort developed AKI compared to 1006 patients (49.4%) who did not develop AKI in the first 48 h. Patient demographics and clinical parameters at the time of admission are shown in Table 1.

The AKI group was older than the non-AKI groups, and had a significantly higher proportion of hypertensive and diabetic patients (*P* = 0.003 and < 0.001 respectively). Other comorbidities such as peripheral vascular disease, ischemic heart disease and chronic obstructive airway disease were not significantly different (*P* = 0.58, 0.24 and 0.07 respectively). The AKI group, compared to the non-AKI group, was sicker based on the lower systolic, diastolic and mean arterial pressures and a higher APACHE III and SAPS II scores. Moreover, patients who developed AKI were more likely to require

Table 2 Comparison of laboratory characteristics at the time of admission to intensive care

	NO AKI (<i>n</i> = 1006)	AKI (<i>n</i> = 877)	<i>P</i> value
pH	7.4 (0.08)	7.3 (0.12)	< 0.001
PaCO ₂ (mmHg)	41 (11.3)	40 (13.7)	0.005
PaO ₂ (mmHg)	116 (85.4)	113 (79.7)	0.5
HCO ₃ (mmol/L)	23.5 (3.7)	20.1 (5.3)	< 0.001
Sodium (mmol/L)	141 (4.2)	141 (5.3)	0.7
Potassium (mmol/L)	4.5 (0.6)	4.7 (0.8)	< 0.001
Urea (μmol/L)	6.2 (3.9)	14.4 (10.6)	< 0.0001
Baseline Creatinine (μmol/L)	72 (36.8)	180 (173.6)	< 0.001
Peak creatinine (μmol/L) ¹	76 (36.6)	196 (175.3)	< 0.001
Serum albumin (g/L)	35 (6.1)	34 (6.1)	0.001
Blood glucose (mmol/L)	8.9 (3.4)	11.1 (5.7)	< 0.001
Lactate (mmol/L)	2.1 (2.0)	3.4 (3.1)	< 0.001
White cell count (× 10 ⁹ /L)	12.9 (9.6)	15.6 (10.8)	< 0.001
Hematocrit (%)	0.36 (0.057)	0.34 (0.061)	< 0.001

¹During first 48 h of ICU admission. Data are presented in mean ± SD. ICU: Intensive care unit.

mechanical ventilation (51.5% vs 46.0%, *P* = 0.01). Patients who developed AKI were more acidotic with lower serum bicarbonate (20.1 mmol/L vs 23.5 mmol/L, *P* < 0.001) and higher lactate (3.4 mmol/L vs 2.1 mmol/L, *P* < 0.001) (Table 2).

The AKI group was sub-classified into 3 categories as per the grade of the renal impairment. Stage 1, 2 and 3 respectively had a serum bicarbonate of 20.8 ± 5.1, 18.2 ± 5.0 and 17.2 ± 6.3 mmol/L. There were however no significant differences in the death rates in ICU across the 3 groups.

In terms of morbidity and mortality, the AKI group had longer ICU and hospital duration and a higher ICU and hospital mortality (Table 3). The multi-regression analysis of independent variables showed that serum bicarbonate on admission (OR = 0.821; 95%CI: 0.796-0.846; *P* < 0.0001), APACHE III (Odds ratio 1.011; 95% CI 1.007-1.015; *P* < 0.0001), age (OR = 1.016; 95%CI: 1.008-1.024; *P* < 0.0001) and presence of sepsis at ICU admission (OR = 2.819; 95%CI: 2.122-23.744; *P* = 0.004) were each significant independent predictors of AKI. The area under the ROC curve was 0.8 (Figure 1) confirming the discriminatory power of the model for predicting AKI.

DISCUSSION

Our study is amongst the first studies investigating whether serum bicarbonate predicts the development of AKI in unselected critically ill ICU patients, in whom AKI aetiology and timing are often unclear. We demonstrated that patients who developed AKI were more acidotic with a lower serum bicarbonate. Hence our study proved that in an ICU setting, serum bicarbonate on admission can be used to make an early diagnosis of AKI. Patients with more severe AKI were more acidotic, although the mortality across the sub-groups of AKI severity did

Table 3 Comparison of outcomes

	NO AKI (<i>n</i> = 1006)	AKI (<i>n</i> = 877)	<i>P</i> value
Died in hospital (%)	30.9	69.1	< 0.001
Death in ICU (%)	57.0	43.0	< 0.001
Hospital length of stay (d)	12.6 (20.1)	14.5 (16.3)	0.02
ICU length of stay (d)	2.8 (4.1)	4.4 (5.7)	< 0.001

Data are presented in mean ± SD. ICU: Intensive care unit.

not significantly differ. Also, serum lactate levels on ICU admission did not predict the onset of AKI. We also found that AKI significantly increased morbidity and mortality, hence highlighting the need for an early diagnostic tool.

The rationale behind the association between AKI and low serum bicarbonate levels can be extrapolated from previous studies which have explored the benefits of sodium bicarbonate in reducing the risk of AKI^[13-17]. Most of those have been performed in a cardiac surgery setting because of the ability to prospectively follow patients before and after a well-timed renal insult. Haase *et al.*^[15] designed a double-blind, randomized controlled trial in patients undergoing cardiac surgery, and found that sodium bicarbonate treatment was associated with an absolute risk reduction for AKI of 20% and with a significant attenuation in the postoperative increase of plasma urea, urinary NGAL and urinary NGAL/urinary creatinine ratio^[15]. It is thought that sodium bicarbonate contributes to increasing oxygen delivery to the renal medulla, while reducing iron-mediated free radical formation due to neutralizing acidosis in this vulnerable region of the kidney^[18]. Therefore, it can be argued that a lower serum bicarbonate level would increase the risk of ischemic injury to the kidneys, especially in a critical illness setting. This logic would support our findings and current model.

Of late, there has been a lot of interest in identifying novel serum and urinary biomarkers which would be more sensitive in predicting AKI. This is because serum creatinine has a poor predictive accuracy for renal injury, particularly in the early stages of AKI^[19]. Our study supports the use of serum bicarbonate, an easily accessible parameter, usually readily available in all patients. Other markers which have been used as predictors of AKI are NGAL, kidney injury molecule-1, Cystatin C, IL-6, IL-8, IL-18, N-acetyl-glucosaminidase, glutathione transferases and liver fatty acid binding protein. However, there is still a lot of debate about their reliability. For example, a wide range of predictive value of NGAL has been only reported across observational cohort studies^[20,21]. Also a clear cut off NGAL concentration for the detection of AKI has not yet been reported, whilst the predictive value of urinary Cystatin C should be interpreted with caution in pre-renal AKI^[22]. More recently, a review

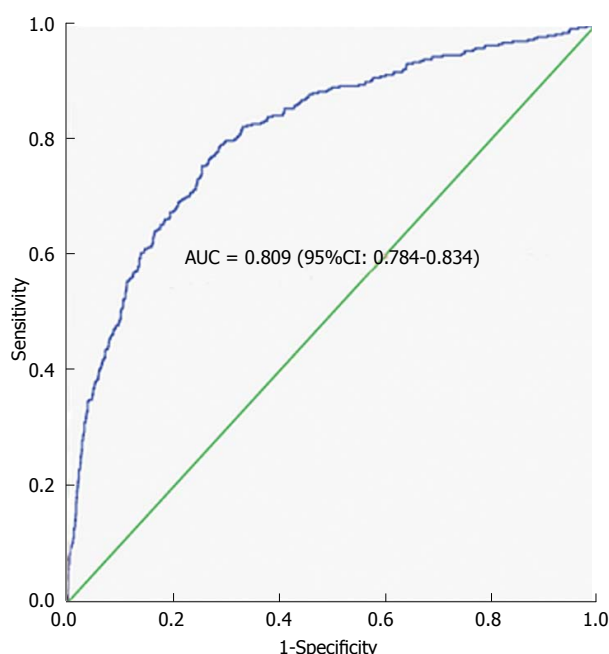


Figure 1 Receiver operating characteristic curve of the final model (including age, sepsis, serum bicarbonate and APACHE III score) predicting acute kidney injury. AUC: Area under the curve.

emphasized on the cumbersome nature of these markers, especially in those settings where timing and aetiology of AKI are not well defined^[23]. Hence, we support the use of serum bicarbonate as an inexpensive and potentially reliable predictor of AKI.

We do acknowledge the limitations of our study. It is a retrospective study with limitations on the selection of patients and the quality of the data. Nevertheless we aimed to include all patients admitted to ICU to reduce the selection bias and all data was collected by two investigators independently and in duplicate using a standardised spread sheet to ensure accuracy. Also, although 7.5% of our cohort had to be excluded from the study due to the unavailability of a baseline creatinine, they were not demographically different to the rest of the cohort.

This study showed that serum bicarbonate at admission may be a predictor of developing AKI in a mixed ICU setting. The current findings can allow timely patient management decisions, including withholding nephrotoxic agents, administration of putative therapeutic agents, and the initiation of RRT since a bicarbonate level is cheap and readily available.

COMMENTS

Background

Metabolic acidosis is often associated with acute kidney injury (AKI) and can result in multiple complications, including cardiac dysfunction, hypotension and mortality. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an intensive care unit (ICU) setting.

Research frontiers

A more thorough understanding of the impact and association of different risk factors with AKI is very important for designing predictive models of patients at high risk of developing this lethal condition, in order that preventative strategies may be created to benefit such a group. Predictive models for development of AKI already exist in cardiac-surgery critically ill patients. There is however a lack of meaningful predictive models in mixed and medical ICUs.

Innovations and breakthroughs

Multiple biomarkers including serum and urinary CysC, NGAL and interleukin-18 have been used to predict AKI. The usefulness of these serum biomarkers in predicting the development of AKI appears to be evolving. Yet assay of these biomarkers are currently expensive and the facilities to assay these biomarkers are not widely available. There is however, a paucity of data regarding the value of metabolic acidosis, especially serum bicarbonate, in making an early diagnosis of AKI in an ICU setting.

Applications

The current study found that serum bicarbonate measured in the early phases of admission to ICU could be used to make an early diagnosis of AKI. Serum bicarbonate measurement is inexpensive and easily available, hence making it an easy test available to anticipate AKI, hence launch the necessary treatment promptly.

Peer-review

This study investigates the utility of serum bicarbonate as a marker of acute kidney injury.

REFERENCES

- 1 **Khwaja A.** KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468]
- 2 **Hoste EA, De Corte W.** AKI patients have worse long-term outcomes, especially in the immediate post-ICU period. *Crit Care* 2012; **16**: 148 [PMID: 22958588 DOI: 10.1186/cc11470]
- 3 **Hewitt J, Uniacke M, Hansi NK, Venkat-Raman G, McCarthy K.** Sodium bicarbonate supplements for treating acute kidney injury. *Cochrane Database Syst Rev* 2012; **6**: CD009204 [PMID: 22696382 DOI: 10.1002/14651858.CD009204.pub2]
- 4 **Fortescue EB, Bates DW, Chertow GM.** Predicting acute renal failure after coronary bypass surgery: cross-validation of two risk-stratification algorithms. *Kidney Int* 2000; **57**: 2594-2602 [PMID: 10844629]
- 5 **Eriksen BO, Hoff KR, Solberg S.** Prediction of acute renal failure after cardiac surgery: retrospective cross-validation of a clinical algorithm. *Nephrol Dial Transplant* 2003; **18**: 77-81 [PMID: 12480963]
- 6 **Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, Ferguson TB, Peterson ED.** Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* 2006; **114**: 2208-2216; quiz 2208 [PMID: 17088458]
- 7 **Abosaif NY, Tolba YA, Heap M, Russell J, El Nahas AM.** The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am J Kidney Dis* 2005; **46**: 1038-1048 [PMID: 16310569]
- 8 **Kolhe NV, Stevens PE, Crowe AV, Lipkin GW, Harrison DA.** Case mix, outcome and activity for patients with severe acute kidney injury during the first 24 hours after admission to an adult, general critical care unit: application of predictive models from a secondary analysis of the ICNARC Case Mix Programme database. *Crit Care* 2008; **12** Suppl 1: S2 [PMID: 19105800 DOI: 10.1186/cc7003]
- 9 **Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A.** Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1012-1024 [PMID: 19850388 DOI: 10.1053/j.ajkd.2009.07.020]
- 10 **Acute Kidney Injury Work Group.** Kidney Disease: Improving Global Outcomes (KDIGO) - Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter* 2012; **2**: 1-138
- 11 **Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A.**

- The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619-1636 [PMID: 1959406]
- 12 **Le Gall JR**, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957-2963 [PMID: 8254858]
 - 13 **Calvert S**, Shaw A. Perioperative acute kidney injury. *Perioper Med (Lond)* 2012; **1**: 6 [PMID: 24764522 DOI: 10.1186/2047-0525-1-6]
 - 14 **Mao H**, Katz N, Ariyanon W, Blanca-Martos L, Adýbelli Z, Giuliani A, Danesi TH, Kim JC, Nayak A, Neri M, Virzi GM, Brocca A, Scalzotto E, Salvador L, Ronco C. Cardiac surgery-associated acute kidney injury. *Cardiorenal Med* 2013; **3**: 178-199 [PMID: 24454314 DOI: 10.1159/000353134]
 - 15 **Haase M**, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Reade MC, Bagshaw SM, Seevanayagam N, Seevanayagam S, Doolan L, Buxton B, Dragun D. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. *Crit Care Med* 2009; **37**: 39-47 [PMID: 19112278 DOI: 10.1097/CCM.0b013e318193216f]
 - 16 **Haase M**, Haase-Fielitz A, Plass M, Kuppe H, Hetzer R, Hannon C, Murray PT, Bailey MJ, Bellomo R, Bagshaw SM. Prophylactic perioperative sodium bicarbonate to prevent acute kidney injury following open heart surgery: a multicenter double-blinded randomized controlled trial. *PLoS Med* 2013; **10**: e1001426 [PMID: 23610561 DOI: 10.1371/journal.pmed.1001426]
 - 17 **Heringlake M**, Heinze H, Schubert M, Nowak Y, Guder J, Kleinebrahm M, Paarmann H, Hanke T, Schön J. A perioperative infusion of sodium bicarbonate does not improve renal function in cardiac surgery patients: a prospective observational cohort study. *Crit Care* 2012; **16**: R156 [PMID: 22898367 DOI: 10.1186/cc11476]
 - 18 **Atkins JL**. Effect of sodium bicarbonate preloading on ischemic renal failure. *Nephron* 1986; **44**: 70-74 [PMID: 3018600]
 - 19 **Drawz PE**, Miller RT, Sehgal AR. Predicting hospital-acquired acute kidney injury--a case-controlled study. *Ren Fail* 2008; **30**: 848-855 [PMID: 18925522 DOI: 10.1080/08860220802356515]
 - 20 **Waikar SS**, Betensky RA, Bonventre JV. Creatinine as the gold standard for kidney injury biomarker studies? *Nephrol Dial Transplant* 2009; **24**: 3263-3265 [PMID: 19736243 DOI: 10.1093/ndt/gfp428]
 - 21 **Mishra J**, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; **365**: 1231-1238 [PMID: 15811456]
 - 22 **Haase-Fielitz A**, Bellomo R, Devarajan P, Bennett M, Story D, Matalanis G, Frei U, Dragun D, Haase M. The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. *Nephrol Dial Transplant* 2009; **24**: 3349-3354 [PMID: 19474273 DOI: 10.1093/ndt/gfp234]
 - 23 **Vanmassenhove J**, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. *Nephrol Dial Transplant* 2013; **28**: 254-273 [PMID: 23115326 DOI: 10.1093/ndt/gfs380]

P- Reviewer: Olowu WA, Pickering JW **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL



Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: A systematic review

Aida Field-Ridley, Viyeka Sethi, Shweta Murthi, Kiran Nandalike, Su-Ting T Li

Aida Field-Ridley, Viyeka Sethi, Shweta Murthi, Kiran Nandalike, Su-Ting T Li, Department of Pediatrics, University of California Davis, Sacramento, CA 95618, United States

Author contributions: All authors contributed to this manuscript. Supported by The National Center for Advancing Translational Sciences, National Institutes of Health, No. UL1 TR000002 (to Dr. Field-Ridley).

Conflict-of-interest: The authors have no conflicts of interest to disclose.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at su-ting.li@ucdmc.ucdavis.edu.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Su-Ting T Li, MD, MPH, Department of Pediatrics, University of California Davis, 2516 Stockton Blvd, Sacramento, CA 95618,

United States. su-ting.li@ucdmc.ucdavis.edu

Telephone: +1-916-7342428

Fax: +1-916-7340342

Received: October 18, 2014

Peer-review started: October 21, 2014

First decision: November 27, 2014

Revised: December 16, 2014

Accepted: January 9, 2015

Article in press: January 12, 2015

Published online: February 4, 2015

and EMBASE databases through July 2014 for English language publications studying FFB performed in the intensive care unit in children < 18 years old. We identified 666 studies, of which 89 full-text studies were screened for further review. Two reviewers independently determined that 27 of these studies met inclusion criteria and extracted data. We examined the diagnostic yield of FFB among upper and lower airway evaluations, as well as the utility of bronchoalveolar lavage (BAL).

RESULTS: We found that FFB led to a change in medical management in 28.9% (range 21.9%-69.2%) of critically ill children. The diagnostic yield of FFB was 82% (range 45.2%-100%). Infectious organisms were identified in 25.7% (17.6%-75%) of BALs performed, resulting in a change of antimicrobial management in 19.1% (range: 12.2%-75%). FFB successfully re-expanded atelectasis or removed mucus plugs in 60.3% (range: 23.8%-100%) of patients with atelectasis. Adverse events were reported in 12.9% (range: 0.5%-71.4%) of patients. The most common adverse effects of FFB were transient hypotension, hypoxia and/or bradycardia that resolved with minimal intervention, such as oxygen supplementation or removal of the bronchoscope. Serious adverse events were uncommon; 2.1% of adverse events required intervention such as bag-mask ventilation or intubation and atropine for hypoxia and bradycardia, normal saline boluses for hypotension, or lavage and suctioning for hemorrhage.

CONCLUSION: FFB is safe and effective for diagnostic and therapeutic use in critically ill pediatric patients.

Key words: Bronchoscopy; Critical illness; Pediatrics; Bronchoalveolar lavage; Pulmonary disease

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Flexible fiberoptic bronchoscopy (FFB) is effective and safe for diagnostic and therapeutic use

Abstract

AIM: To investigate the diagnostic yield, therapeutic efficacy, and rate of adverse events related to flexible fiberoptic bronchoscopy (FFB) in critically ill children.

METHODS: We searched PubMed, SCOPUS, OVID,

among critically ill pediatric patients. FFB led to change in management in 28.9% of patients, with a diagnostic yield of 82%. Bronchoalveolar lavage obtained during FFB may assist with identifying infectious organisms (25.7%) and optimizing antimicrobial therapy (19.1%). FFB had therapeutic benefit with removal of mucus plugs or resolution of atelectasis in 60.3%. The majority of reported adverse events were transient and included hypotension, hypoxia and/or bradycardia requiring minimal intervention.

Field-Ridley A, Sethi V, Murthi S, Nandalike K, Li STT. Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: A systematic review. *World J Crit Care Med* 2015; 4(1): 77-88 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/77.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.77>

INTRODUCTION

Flexible fiberoptic bronchoscopy (FFB) is recognized as an essential tool to diagnose and treat pediatric pulmonary disorders. Even though the first published report on the utility of FFB in children was in 1978, rigid bronchoscopy by surgeons remained standard of practice for many years due to instrument size limitations^[1,2]. With the advent of smaller-sized bronchoscopes, FFB use has increased in pediatric and neonatal patients^[3-6].

In 1987, the first published FFB guideline for adults provided recommendations for the use of bronchoscopy for diagnosis and management of a broad spectrum of inflammatory, infectious, and malignant diseases^[7]. Updated guidelines published by the British Thoracic Society further defined the indications, patient selection criteria, and potential adverse events in adult bronchoscopy^[8]. However, the guidelines for adult FFB cannot necessarily be extrapolated to children given the smaller airways, differences in pulmonary diagnoses, and sedation needs for FFB in children. Guidelines about the use of FFB in pediatric patients are over a decade old^[9,10]. Despite increased use of FFB by pediatric pulmonologists, intensivists and anesthesiologists, there are no current guidelines regarding the safety and utility of FFB in the pediatric critically ill population.

Our objective was to systematically review the published literature on the utility and safety of FFB in pediatric and neonatal intensive care settings. Our specific questions were: (1) what is the diagnostic yield of FFB; (2) what is the therapeutic efficacy of FFB; and (3) what is the rate of adverse events secondary to FFB?

MATERIALS AND METHODS

This systematic review was conducted according to

PRISMA guidelines^[11]. The protocol for our study was registered online at PROSPERO (CRD42014010801)^[12]. The National Library of Medicine through PubMed was searched for "bronchoscopy" (MeSH and all fields) and "intensive care units" (MeSH and all fields) and English and "journal article" AND infant (MeSH) or child (MeSH) or adolescent (MeSH). In addition, we searched the following databases for the terms "bronchoscopy" and "intensive care unit" and (infant or child or adolescent) and "journal article" and English language: SCOPUS, OVID, and EMBASE. Our search strategy included studies published in English from database inception to July 20, 2014. References of identified articles were searched for additional relevant articles.

Articles eligible for inclusion were English-language manuscripts reporting either diagnostic, therapeutic or adverse events related to FFB performed on children (< 18 years old) in intensive care units (ICUs). Cohort, case control, or randomized controlled trials that reported either diagnostic, therapeutic, or adverse events related to FFB were included. Articles focusing on bronchoscopy in patients with foreign body aspiration were excluded, as rigid bronchoscopy is indicated for removal of foreign bodies^[9]. For the purposes of this systematic review, we defined a positive diagnostic FFB as one identifying anatomic or functional airway abnormality, foreign body/obstruction, mucus plugging/atelectasis, hemorrhage, and/or airway inflammation.

One author (SM) screened article titles for initial inclusion. Two authors (SM and SL) independently screened abstracts in duplicate for inclusion. All authors (SM, SL, AF, VS and KN) piloted the standardized electronic data extraction form on two articles. Two authors independently assessed each article for study eligibility and extracted data. Data extracted included study design, participant demographics, and bronchoscopy outcomes (including diagnostic results, change in therapy, bronchoalveolar lavage (BAL) results, ICU length of stay, hospital length of stay, length of mechanical ventilation, rate of successful extubation, and adverse events). Risk of bias was not assessed. Discrepancies were resolved after joint article review and discussion. Results were presented as a narrative synthesis. Pooled estimates of diagnostic yield, therapeutic efficacy, and adverse events were estimated as weighted averages with weights proportional to study denominators from the relevant subpopulations, making the assumption that study-specific proportions are homogeneous. No formal tests for homogeneity were conducted in light of the wide variation in denominator counts, including very small studies^[13].

Statistical analysis

The statistical methods of this study were reviewed by Daniel J. Tancredi, PhD, from the University of

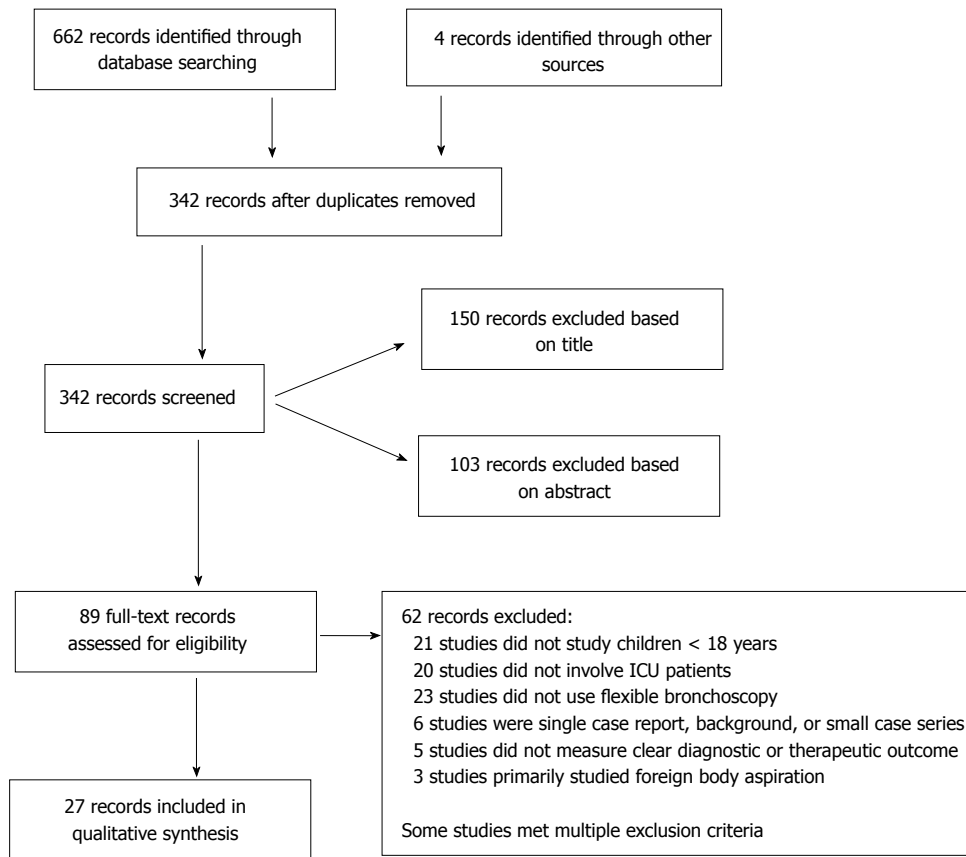


Figure 1 Flow diagram of the study selection process. ICU: Intensive care unit.

California Davis.

RESULTS

Study characteristics

We identified 666 studies, of which 89 full-text studies were screened for further review. Two reviewers independently determined that 27 of these studies met inclusion criteria (Figure 1).

Two-thirds of the included studies were retrospective cohort, the remainder consisted of case control or prospective cohort studies (Table 1). Sixteen studies (59%) investigated patients admitted to a pediatric intensive care unit (PICU), eight studies (30%) investigated neonatal intensive care Unit (NICU) patients, while three (11%) included both PICU and NICU patients. Almost all FFB were performed at the bedside, with the exception of routine evaluation for esophageal atresia, where the procedure took place in the operating room^[14]. The patient populations undergoing FFB included patients evaluated for a spectrum of anatomic airway or intrinsic pulmonary abnormalities, including patients with congenital heart disease (CHD) (7/27; 26% studies) and patients on extracorporeal life support (ECLS) (4/27; 15% studies)^[4,15-23]. FFB was performed multiple times on patients in 55% of the studies.

Diagnostic yield of FFB

Six studies reported a change in clinical management secondary to FFB in 28.9% (range 21.9%-69.2%; 157/540)^[4,14-16,24]. Changes in clinical management included unanticipated surgical intervention, modification of surgical intervention, and alteration of endotracheal suctioning techniques. The change in clinical management due to FFB findings was similar for non-surgical patients (22.3%; range 18.5%-69.2%; 82/368) and lower for airway surgery patients (8.9%; range 3.4%-24.2%; 42/472). Atzori *et al.*^[14] reported that FFB was instrumental in delineating the type of tracheoesophageal fistula and altered surgical planning in 24.2% (15/62) of children with esophageal atresia^[14]. De Blic *et al.*^[4] reported that in children with CHD, FFB findings of external compression of the airways by cardiovascular anomalies prompted earlier cardiac surgery in 50% (5/10)^[4].

Twenty-one studies reported an overall diagnostic yield of 82% using FFB (range 45.2%-100%; 3791/4622)^[3-5,14-18,20-33]. FFB was more likely to be positive in patients with suspected upper airway abnormalities (92.7%; range 73%-95.2%; 858/926) than in patients with suspected lower airway abnormalities (74.3%; range 11.3%-90.2%; 2274/3061). Upper airway findings included airway stenosis, compression or malacia, edema, foreign body, pseudomembrane,

Table 1 Indications, diagnostic, and therapeutic outcomes for flexible bronchoscopy in critically ill pediatric patients

Ref.	Population	Indications	Diagnostic yield	Diagnostic BAL findings	Therapeutic outcomes
Abu-Kishk <i>et al</i> ^[25] , 2012	9 PICU: hemoptysis (age 2 mo-17 yr)	Hemoptysis	77.8% (7/9)		
Atzori <i>et al</i> ^[14] , 2006	62 NICU: esophageal atresia (mean age 37.5 WGA)	Airway evaluation	24.2% (15/62): Change in surgical management 9.7% (6/62): Change in anatomic class 11.3% (7/62): Tracheomalacia		
Bar-Zohar <i>et al</i> ^[24] , 2004	100 PICU: medical, non-airway surgery, and airway surgery groups (age 2 d-17 yr)	Airway evaluation; BAL; extubation failure	73% (65/89): Upper airway 56% (14/25): Lower airway 63.6% (28/44): Extubation failure 38.6% (44/114): Change in medical management 20% (11/31): Airway surgical re-exploration	46.7% (14/30) identified organism 50% (15/30) change in antimicrobials 40% (12/30) clinical improvement after change in antimicrobials 36.4% (4/11) concordance between BAL and blind tracheal aspirate 33.3% (2/6) identified organisms in patients with mucosal inflammation	84.6% (11/13) extubated after lavage 74.3% (26/35) re-expanded collapsed lobe
Chapotte <i>et al</i> ^[18] , 1998	72 PICU: CHD (age 1 d-14 yr)	Perioperative evaluation; respiratory symptoms; radiologic respiratory signs	70.8% (51/72) 48.6% (35/72) identified extra-luminal compression		
Davidson <i>et al</i> ^[17] , 2008	129 PICU: ECLS, CHD (age 2.9 mo-3 yr)	Airway evaluation; atelectasis; BAL; ETT position; respiratory distress	68.4% (78/114): Overall 46.3% (37/80): ECLS 60.3% (41/68): CHD identified extra-luminal compression	45.3% (53/117): Overall identified organism 53.8% (28/52): ECLS subgroup identified organism	82.1% (32/39) successful procedures: removed blood and mucous plugs, or instilled surfactant, placed endovascular stents
de Blic <i>et al</i> ^[4] , 1991	33 NICU: CHD, lung disease and/or congenital malformations (age 2 d-9 mo)	Anatomic evaluation; atelectasis/emphysema; respiratory distress	62.2% (23/37): Overall 52.8% (19/36): Change in management 13.9% (5/36): Change in surgical management 50% (5/10): CHD		
Efrati <i>et al</i> ^[16] , 2009	319 PICU: CHD, oncology (age 1-22 yr)	Anatomic evaluation; BAL; trauma	79.3% (253/319): Overall 90.2% (46/51): CHD 83.3% (50/60): Oncology 21.9% (70/319): Change in management 3.4% (11/319): Change in surgical management 94.8% (91/96)	17.6% (56/319): Identified organism 12.2% (39/319): Change in antimicrobials 88% (22/25): Abnormal cytology consistent with infection	
Fan <i>et al</i> ^[26] , 1988	87 PICU: (age 1 wk-18 yr)	Anatomic evaluation; decannulation; difficult intubation; respiratory symptoms; tracheostomy			87.5% (7/8) 100% (5/5): Difficult airways intubated 66.7% (2/3): Re-expanded collapsed lobe
Hintz <i>et al</i> ^[22] , 2002	8 NICU: CDH on ECLS	Atelectasis			87.5% (7/8): Improved lung expansion after lavage
Kamat <i>et al</i> ^[19] , 2011	79 PICU: ECLS (10 d-21 yr)	Atelectasis; BAL; anatomic evaluation; surfactant instillation		21.3% (33/155): Identified organism	76.1% (118/155): Atelectasis 15.4% (10/65): Improved CXR 2.6% (4/155): Surfactant
Kohelet <i>et al</i> ^[27] , 2011	19 NICU: (age 1 d-8 mo)	Anatomic evaluation; atelectasis; BAL; difficulty weaning MV; respiratory symptoms	60% (15/25): Overall 100% (6/6): Wean from MV 52% (13/25): Abnormal anatomy	60% (6/10): Identified organism 50% (5/10): Change in antimicrobials	75% (6/8): Re-expanded collapsed lobe
Kolat <i>et al</i> ^[28] , 2002	45 NICU: (mean age 33 WGA)	Respiratory distress post-extubation	93.3% (42/45)		

Kotby <i>et al</i> ^[29] , 2008	35 PICU: suspected pulmonary fungal infections (age 1-15 yr)	BAL		40% (14/35): Identified organism 77.1% (27/35): Diagnosed probable pulmonary fungal infection (+ BAL culture or + BAL fungal antigen)	
Maggi <i>et al</i> ^[36] , 2012	44 PICU: status asthmaticus requiring MV (age 6 mo-18 yr)	Atelectasis; lavage; respiratory distress;			100% (29/29): Improved A-a gradient, shunt fraction, decreased FiO ₂ , improved compliance. 37.9% (11/29): Extubated within 6 h 69% (20/29): Extubated within 12 h Reduced PICU LOS (3.06 d vs 3.4 d in control ($P < 0.05$)) Reduced length of time on MV [10 h vs 20.5 h ($P < 0.0005$)]
Manna <i>et al</i> ^[30] , 2006	134 PICU: CHD (age 4 mo-6 yr)	Anatomic evaluation; atelectasis; BAL; extubation failure; hemorrhage	76.4% (113/148): Overall 84.4% (27/32): Upper airway 80% (56/70): Lower airway 18.6% (13/70): CHD identified extraluminal compression 90.5% (19/21): Extubation failure 44% (11/25): Pulmonary disease 50% (5/10): Overall 20% (2/10): Granuloma	35.3% (6/17): Identified organism	92.3% (24/26): Re-expanded collapsed lobe
Myer <i>et al</i> ^[30] , 1988	10 NICU: (age 1 d-16 mo)	Atelectasis; hemorrhage; hypercarbia; hypoxia; hyperinflation; respiratory distress			60% (3/5): Re-expanded collapsed lobe 40% (2/5): Granuloma required rigid bronchoscopy
Nakano <i>et al</i> ^[5] , 2004	16 NICU: esophageal atresia, Trisomy 21, CDH, hydrocephalus, Goldenhaar, and Kasabach-Merritt (age 3 d-8.5 mo)	Anatomic evaluation; extubation failure; hemorrhage; respiratory distress	66.7% (14/21)		23.8% (5/21): Removed obstruction (mucus plug, clot/local tissue) or altered suction practice
Nayak <i>et al</i> ^[21] , 2012	30 PICU: CHD requiring mechanical ventilation prior to extubation (age 1 d-6 mo)	Anatomic evaluation; extubation failure	50% (15/30): Overall significant tracheobronchial narrowing 50% (4/8): Extubation failure		73.3% (22/30): Extubated
Nussbaum <i>et al</i> ^[31] , 2002	2836 PICU: (age 1 d-15 yr)	Anatomic evaluation; atelectasis; BAL; hemorrhage; ETT position; intubation; tracheostomy evaluation; plastic bronchitis; respiratory distress	84.8% (2405/2836): Overall 95.2% (766/805): Upper airway 82.6% (1862/2254): Lower airway 47.9% (1358/2836): Inflammatory changes	24.1% (411/1705): Identified organism 41.7% (5/12): Transbronchial biopsy positive dyskinetic cilia syndrome 72.4% (21/29): Acute chest SCD plastic bronchitis	
Peng <i>et al</i> ^[32] , 2011	358 PICU and NICU: (age 1 d-17.5 yr)	Anatomic evaluation; BAL; intubation; respiratory distress	87.2% (312/358): Overall 47.8% (171/358): Airway malacia 39.4% (141/358): Inflammatory changes		56.1% (201/358): Interventional FFB 71.4% (518/725): of all FFB were interventional 66.7% (10/15): Survived after removal of debris
Pietsch <i>et al</i> ^[37] , 1985	19 NICU: necrotizing tracheobronchitis (mean age 6.53 d)	Therapeutic removal of obstruction			

Prentice <i>et al</i> ^[23] , 2011	7 PICU: ECLS (age 8 d-27 yr)	Persistent atelectasis	57.1% (4/7): Bronchus compression/narrowing 71.4% (5/7): Mucus plugs	100% (7/7)	75% (3/4): Identified organism 75% (3/4): Change in antimicrobials 65% (26/40): Identified organism	28.7% (2/7): Removed mucus plugs, ECLS subsequently weaned
Sachdev <i>et al</i> ^[35] , 2010	30 PICU: clinical suspicion of VAP (age 1 mo-12 yr)	BAL				
Soong <i>et al</i> ^[43] , 2011	8 PICU and NICU: obstructive fibrinous tracheal pseudomembrane (age 2 mo-13 yr)	Therapeutic ablation				100% (8/8): Ablation of obstructive membrane
Soong <i>et al</i> ^[33] , 1995	207 NICU and PICU: (age 1 d-10 yr)	Respiratory symptoms; intractable pneumonia		81.1% (172/212)		35.4% (75/212): Resolution of atelectasis, improved secretions
Tang <i>et al</i> ^[3] , 2009	47 PICU: (age 1 d-13 yr)	Anatomic evaluation, BAL; therapeutic (FB, clot removal, hemoptysis, intubation)		80.9% (38/47)	36.8% (7/19): Identified organism 57.9% (11/19): Change in antimicrobials	87.0% (20/23): Re-expanded collapsed lobe. 44.8% (13/29): Extubated < 24 h after mucus plug, blood clot, FB removed
Ward <i>et al</i> ^[15] , 1987	25 PICU: CHD (n = 7), (age 1 d-11 yr)	Anatomic evaluation; atelectasis; confirm ETT/tracheostomy position; hyperinflation; respiratory distress	62.5% (5/8): Tracheostomy - change in management 80% (4/5): Hemoptysis - change in management 85.7% (6/7): CHD	64% (16/25): Overall		

A-a gradient: Alveolar-arterial gradient; ARDS: Acute respiratory distress syndrome; BAL: Bronchoalveolar lavage; CDH: Congenital diaphragmatic hernia; CHD: Congenital heart disease; CXR: Chest X-ray; ECLS: Extracorporeal life support; ETT: Endotracheal tube; FB: Foreign body; FFB: Flexible fiberoptic bronchoscopy; FiO₂: Fractional of inspired oxygen; LOS: Length of stay; MV: Mechanical ventilation; NICU: Neonatal intensive care unit; PIC: Pediatric intensive care unit; SCD: Sickle cell disease; TEF: Tracheoesophageal fistula; VAP: Ventilator associated pneumonia; WGA: Weeks gestational age.

and vocal cord dysfunction^[20,24,31]. Lower airway findings included airway stenosis, compression, malacia, mucus plugs, thrombus, and malpositioned endotracheal tube^[3,14,15,17,18,20,21,23,24,31,32].

The diagnostic yield of FFB varied amongst different patient populations. The populations with the highest diagnostic yield of FFB were patients with extubation failure, patients with CHD, patients with hemoptysis, and patients undergoing ECLS. In patients with extubation failure, FFB identified a cause, such as mucus plugs, laryngotracheomalacia, laryngeal trauma/edema or compression, in 69.9% (range 50%-90.5%; 51/73)^[3,16-21,24,27,31,32]. In children with CHD, the diagnostic yield of FFB was 57.5% (range 18.5%-90.2%; 177/308). External airway compression was the most commonly reported finding^[15-18,20,21,34]. In patients with hemoptysis, FFB identified a cause in 56% of patients (range 20%-100%; 14/25)^[5,15,25,30]. In patients receiving ECLS, 31% (range 21.5%-46.2%; 108/349) had a positive finding on FFB, including airway compression, abnormal bronchial anatomy, malpositioned or occluded endotracheal tube, or mucus plugging^[17,19,22,23].

BAL was a common indication for FFB and findings were reported in 12 studies^[3,16-20,23,24,27,29,31,35]. An infectious organism was identified in 25.7% (range 17.6%-75%; 631/2455) of all BALs performed. The

highest yield of BAL was in immunocompromised patients, where 79.1% of BALs were found to be positive (range 42.9%-83.3%; 53/67)^[16,20]. In ECLS patients, BAL identified an organism in 30.3% of procedures (range 21.3%-75%; 64/211)^[17,19,23]. Five studies reported that BAL led to a change in antimicrobial therapy in 19.1% (range 12.2%-75%; 73/382) of patients^[3,16,23,24,27]. Bar-Zohar *et al*^[24] reported that in the 50% (15/30) of patients whose antibiotics were changed as a result of BAL findings, only 33% (10/30) of them improved clinically^[24]. Concordance between BAL isolates and blind tracheal swab isolates was 47% (range 36%-67%; 8/17)^[24,27]. In critically ill children, the use of BAL for non-infectious causes of pulmonary infiltrates was uncommon. Two isolated studies reported findings associated with aspiration in 67% (2/3) of cases and evidence of hemoptysis in 63% (5/8)^[20,24].

Therapeutic efficacy

Therapeutic outcomes were reported in 17 of 27 studies. Overall, the therapeutic yield for FFB was 60.3% (range 23.8%-100%; 595/987). Interventions performed with FFB included lavage, removal of partial obstructions, and assistance with difficult intubations or failed extubations. An improvement in atelectasis after FFB was reported in 44.9% (range 15.4%-92%; 173/385)

of procedures^[3,19,20,22,24,26,27,30,33]. In one study of 44 intubated children with status asthmaticus, FFB, compared to no FFB, was associated with decreased length of time on mechanical ventilation (20.5 h vs 10 h) and decreased PICU length of stay (3.4 d vs 3.1 d), but no change in total hospital length of stay^[36]. In the three studies that examined the utility of FFB in assessing the etiology of extubation failure, FFB assisted in successful extubation in 69.9% of procedures (range 50%-90.5%; 51/73)^[20,21,24] by removing mucus plugs or thrombus to assist with weaning from the ventilator. FFB was also used to identify patients with a normal exam who were ready for extubation^[3,5,15,17,24]. Kohelet *et al.*^[27] found that in neonatal patients, therapeutic FFB in the NICU improved atelectasis in 75% (6/8) and decreased mechanical ventilation time.

Four studies reported the therapeutic yield of FFB in 174 patients receiving ECLS^[17,19,22,23]. In these patients, repeat FFB to re-expand collapsed lobes was successful in 42.9% (range 15.4%-87.5%; 51/119). Furthermore, repeat therapeutic lavage was associated with decreased ventilator support, increased lung expansion and tidal volumes. Improved lung recruitment was associated with reduced ECLS support and, ultimately, separation from ECLS^[17,19,22,23].

Adverse events

Sixteen studies that included 5060 bronchoscopies reported adverse events (Table 2). Overall, adverse events were reported in 12.9% (range 0.5%-71.4%; 654/5060) of FFBs performed. Serious adverse events requiring intervention were uncommon (2.1%; 108/5060). The most common adverse events were hypoxia, bradycardia, hypotension, and bleeding. Mild to moderate hypoxia (with oxygen saturations greater than 80%) was reported in 2.3% (range 0%-70.3%; 114/5060) of FFBs and usually resolved with removal of the FFB from the airway and/or supplemental oxygen^[3,4,16,20,24,26,29,31,32]. In 6.1% (7/114) of patients with hypoxia, bag-mask ventilation was required for recovery. Bradycardia with hypoxia was reported in 0.4% (range 0%-4%; 21/5060) of FFBs performed^[16,24,26,27,31-33]. A single study reported that 3.4% (11/319) of patients required atropine to treat bradycardia in addition to supplemental oxygen for hypoxia^[16]. Hypotension occurred in 1.2% (range 0%-19.4%; 58/5060) of procedures performed, and a fluid bolus was given in 0.9% (46/5060) of all procedures^[20,24,29]. Bleeding occurred in 4% (range 0%-37.5%; 198/5060) of overall procedures performed, and in most cases, resolved spontaneously or with suction^[3,16,22,23,29,31,33]. In the 0.4% (range 0.4%-5.9%; 21/5060) of procedures that required intervention for hemostasis, saline or epinephrine lavage was sufficient to stop bleeding^[16,19,23,31]. In patients receiving ECLS, who are at higher risk for bleeding secondary to

systemic anticoagulation, 15.9% (range 0%-37.5%; 60/260) had bleeding after FFB^[19,23]. Other reported complications included local trauma, such as pneumothorax or perforation (0.2%; 8/5060), stridor (0.3%; 14/5060), bronchospasm (0.5%; 24/5060), and fever (4.1%; 217/5060). Data on specific anesthetic risks were rarely reported. Three patients (0.1%; 3/2984), who received fentanyl in preparation for FFB, had rigid chest, and two of the three required intubation^[20,23]. Two deaths were reported in high-risk neonates due to perforation of the mainstem bronchus. Both infants were subsequently found to have full thickness necrotizing tracheobronchitis^[37].

DISCUSSION

FFB contributes to changes in clinical management, can assist in the diagnosis of upper and lower anatomic lesions of the respiratory tract, and is integral in identifying causes of respiratory distress and prolonged mechanical ventilation. Furthermore, FFB can be used for therapeutic interventions such as removal of obstructions and re-expansion of collapsed lung. Despite a consensus statement adopted by the American Thoracic Society in 1991, and guidelines by the European Respiratory Journal in 2003, there are no specific guidelines for FFB in critically ill pediatric and neonatal patients^[9,10]. We have determined that there are populations for whom FFB is a high yield procedure and should be strongly considered (Table 3).

Change in clinical management is an important measure of the utility of FFB. We found that, in more than a third of cases, FFB was integral in changing patient care. This is similar to a study of adult ICU patients, in which 33% (29/87) of FFB led to a change in patient management^[38,39]. We found that FFB significantly contributed to surgical planning in those without known respiratory anomalies, earlier surgical intervention in children with CHD, and change in the type of surgical intervention in children with esophageal atresia. FFB was also important in altering medical management, such as adjusting endotracheal suction techniques after identifying airway granulomas.

The overall diagnostic yield for FFB was 82%. While some studies included inflammation as a significant finding, even when these studies were excluded, the diagnostic yield was 75.2% (range 45.2%-100%; 1074/1428)^[3,31,32]. This is higher than the 44% (44/87) diagnostic yield reported in critically ill adults^[38]. The higher incidence of positive FFB in pediatric ICU patients may be secondary to the reluctance to perform early FFB in children, leading to severe and persistent symptoms prior to FFB. Specific populations in whom there was high diagnostic yield with FFB included children with CHD, children who failed extubation, and children with

Table 2 Adverse events reported with flexible bronchoscopy in critically ill pediatric patients

Ref.	Hypoxia	Bradycardia/ Hypoxia	Hypotension	Hemorrhage	Other
Bar-Zohar <i>et al</i> ^[24] , 2004	0% (0/155)	0% (0/155)	19.3% (30/155) 12.9% (20/155) NS bolus	0% (0/155)	1.3% (2/155) intubated for mucus plug
Davidson <i>et al</i> ^[17] , 2008				0% (0/200)	0.5% (1/200) patient "instability"
de Blic <i>et al</i> ^[4] , 1991	70.3% (26/37) transient moderate hypoxia (SaO ₂ > 80)	0% (0/37)			
Efrati <i>et al</i> ^[16] , 2009	6.6% (21/319), resolved - O ₂ 0.3% (1/319) - BMV 0.3% (1/319) required intubation	3.4% (11/319), resolved - O ₂ and atropine		1.6% (5/319), resolved-saline lavage	1.6% (5/319) stridor resolved -steroids or epinephrine 0.9% (3/319) fever
Fan <i>et al</i> ^[26] , 1988	2.3% (2/87), resolved - removal of scope or O ₂	0% (0/87)			
Hintz <i>et al</i> ^[22] , 2002				37.5% (3/8)	
Kamat <i>et al</i> ^[19] , 2011				34.2% (53/155) mild to moderate blood tinged secretions 2% (3/155) placed on HFOV for increased bloody secretions	
Kohelet <i>et al</i> ^[27] , 2011		Transient (number not reported)	0% (0/25)	0% (0/25)	4% (1/25) pneumothorax
Kotby <i>et al</i> ^[29] , 2008	42.9% (15/35), transient		5.7% (2/35), transient	22.9% (8/35)	Decreased PaO ₂
Manna <i>et al</i> ^[20] , 2006	10.8% (16/148) transient; 16.7% (3/18) of ARDS patients		17.6% (26/148), NS bolus		0.6% (1/148) rigid chest after fentanyl
Nussbaum <i>et al</i> ^[31] , 2002	0.7% (21/2836), of those 76.2% (16/21) resolved - removal of scope or O ₂ ; 23.8% (5/21) emergency intubation; 2/5 apneic prior to FFB	Transient (number not reported)	0% (0/2836)	4% (113/2836) mild nasopharyngeal bleeding 0.4% (12/2836) bleeding after biopsy, resolved - epinephrine lavage	Transient stridor (number not reported) 0.6% (17/2836) laryngo/bronchospasm, resolved - albuterol and O ₂ , BMV 9.5% (2/21) rigid chest after fentanyl
Peng <i>et al</i> ^[32] , 2011	Transient (number not reported)	Transient (number not reported)			0.8% (6/725) laryngospasm, resolved - lidocaine spray and NIPPV 0.3% (2/725) pneumothorax 29.5% (214/725) fever
Pietsch <i>et al</i> ^[37] , 1985					13.3% (2/15) death secondary to mainstem bronchus perforation 6.7% (1/15) pneumothorax - chest tube
Prentice <i>et al</i> ^[23] , 2011				5.9% (1/17), resolved - epinephrine lavage	
Soong <i>et al</i> ^[33] , 1995		4% (10/247) transient, resolved - removal of scope or O ₂ 1.2% (3/247) required BMV		Self-limited nasal bleeding (number not reported)	2% (5/247) stridor
Tang <i>et al</i> ^[3] , 2009	20.8% (11/53), mild			3.8% (2/53), mild	1.9% (1/53) SVT 1.9% (1/53) pneumothorax 1.9% (1/53) bronchospasm

ARDS: Acute respiratory distress syndrome; BMV: Bag mask ventilation; FFB: Flexible fiberoptic bronchoscopy; HFOV: High frequency oscillatory ventilation; NIPPV: Noninvasive positive pressure ventilation; NS: Normal saline; O₂: Oxygen; PaO₂: Arterial partial pressure of oxygen; SVT: Supraventricular tachycardia.

concern for upper airway abnormalities. Therefore, we propose that FFB should be strongly considered in the early evaluation of patients with CHD, children

who failed extubation, and children with suspected upper airway abnormalities (Table 3).

BAL was used to identify causative organisms

Table 3 Recommended indications for flexible bronchoscopy in critically ill children

Recommend	Consider
Upper airway symptoms (e.g., stridor)	CHD with persistent atelectasis
BAL in immunocompromised + respiratory distress	ECLS with persistent atelectasis
BAL in immunocompetent + respiratory distress	Prolonged mechanical ventilation
AND	
+ new/persistent fever	
AND infiltrate on chest X-ray on existing therapy	Esophageal atresia Asthma intubated + persistent atelectasis

BAL: Bronchoalveolar lavage; ECLS: Extracorporeal life support; FFB: Flexible fiberoptic bronchoscopy; CHD: Congenital heart disease.

and tailor antibiotic management. The emergence of antibiotic resistant organisms requires that clinicians have the ability to tailor therapy. Thus, BAL may play a critical role in antibiotic stewardship. The 50% concordance of BAL with blind tracheal aspirates supports the use of BAL rather than blind tracheal aspirates in patients who are not improving on current antibiotic management. We found the highest yield of BAL culture was in patients who are immunocompromised (79%) or had a new fever with infiltrate on chest X-ray. Similar findings have been reported in critically ill adults, where BAL identified an organism in 24% (150/616) of procedures, with the highest yield (36%; 47/129) among immunocompromised patients^[39]. Our findings support the use of FFB to obtain BAL in the immunocompromised host with respiratory insufficiency or in patients with pneumonia not responding to current antibiotic therapy (Table 3). Additional consideration should be given to FFB in the ECLS population^[17,19,23]. In patients receiving ECLS, common clinical signs of infection may be obscured since body temperature is controlled *via* the ECLS circuit and systemic inflammatory response syndrome can be induced by ECLS. A high index of suspicion for infection is warranted in patients receiving ECLS who develop new infiltrates or have difficulty weaning from ECLS support. Therefore, FFB should be considered promptly in these patients.

FFB is an important therapeutic option for patients with respiratory compromise. Overall, greater than 50% of patients who underwent FFB for a therapeutic intervention achieved some benefit. This is similar to adult studies where 44% (range 22%-89%; 64/147) of patients received therapeutic benefit from bronchoscopy^[38,40,41]. In pediatric studies, several specific populations appeared to derive the most benefit from therapeutic FFB. In a single study of patients with respiratory failure from

asthma who underwent FFB, mucus plug removal was associated with improved oxygenation and lung expansion on chest X-ray, reduced ventilator support, and shorter PICU length of stay^[36]. In patients receiving ECLS, FFB was associated with reduced need for ECLS support, particularly when bronchoscopy was performed multiple times. FFB may have the ability to decrease morbidity and mortality associated with prolonged ECLS support since FFB may improve respiratory mechanics and thus need for ECLS^[42]. FFB has only recently become a treatment modality in the NICU with the advent of ultrathin bronchoscopes. An important consideration in this population is the impact of mechanical ventilation on premature and developing lungs. By treating atelectasis and decreasing time on mechanical ventilation, FFB in the NICU may ameliorate subglottic stenosis and chronic lung disease seen with prolonged ventilation. We suggest that therapeutic bronchoscopy be considered in intubated patients with asthma and atelectasis, patients receiving ECLS, and NICU patients with difficulty weaning from mechanical ventilation (Table 3). The recommendation to perform FFB in neonates to evaluate difficulty weaning from mechanical ventilation is in accord with the European Respiratory Journal guidelines, which support the use of FFB in neonates to evaluate for subglottic stenosis and other airway abnormalities. However, recommendations for FFB for asthmatic and ECLS dependent populations are not specified in either the European Respiratory Journal or the American Thoracic Society guidelines^[9,10].

We found that 2.1% of pediatric patients who undergo FFB had adverse events that required a medical intervention, which is similar to the 2% (range 1.6%-4%; 17/814) reported in the adult populations^[38,39]. Interventions were minor, including halting the procedure to allow spontaneous recovery from hypoxia, providing supplemental oxygen, and administering fluid boluses for hypotension. The patient populations with the highest proportion of complications were those receiving ECLS and immunocompromised patients. Patients receiving ECLS were systemically anticoagulated, and had more frequent bleeding complications requiring intervention with suctioning, saline lavage or local epinephrine. Whether the higher proportion of complications in immunocompromised patients is secondary to higher disease burden or directly related to the procedure itself is unclear. Nonetheless, adverse events requiring interventions including bag-mask ventilation and intubation were higher in this group. Due to insufficient data, we were not able to derive any meaningful interpretation regarding adverse events from sedatives used during FFB. In the studies that reported complications related to sedation, the most serious was rigid chest from fentanyl given pre-procedure in three patients who

were not intubated. In our review, studies reported a mix of intubated and non-intubated patients who underwent FFB. While there was not a reported difference in adverse events in those with a secured airway as compared to those with a natural airway, the considerations to undertake the procedure may be different. For example, sedation choices may vary, and consideration of bronchoscope size relative to airway becomes important when the approach is through the nares. Finally, there may be increased risk of adverse events in patients who undergo multiple FFBs, although this finding was not born out in our review.

Limitations

Our study has several limitations. We did not assess study quality in this review. Our inclusion criteria were broad to maximize our assessment of the available literature on the use of flexible bronchoscopy in critically ill children. Thus, the only studies excluded were case reports. We used standard methodology to identify papers to include in our review; however, it is possible that we may have missed publications. We limited our review to papers in English, and may have seen different results in non-English language publications. Included studies did not always distinguish between patients admitted to the ICU for procedural sedation and those that were critically ill. Thus, it is possible that not all patients included in this review were critically ill. Children with foreign body aspiration were excluded from our study because foreign body aspiration should be removed by rigid bronchoscopy.

Many of the included studies did not report quantitative outcomes after FFB, making it difficult to draw conclusions about specific risks or benefits of the procedure (e.g., a study may have mentioned improvement in ventilator settings, but did not quantify this in a meaningful way). Some studies also reported normal examinations as part of their diagnostic yield. Furthermore, one of the concerns regarding the use of FFB in pediatric populations is the anesthetic risk in these patients. According to the pediatric guidelines by the American Thoracic Society, adverse reactions to medications account for at least half of complications associated with FFB^[9]. In many of the included studies, it was difficult to differentiate anesthetic complications from procedural complications. Future studies should examine complications due to sedatives among patients who undergo FFB.

We have identified patient populations in whom FFB should be strongly considered. Given the overall high diagnostic and therapeutic yield, there is a rationale to perform FFB more frequently in critically ill children. Our data suggest that experienced bronchoscopists be readily available to evaluate and treat critically ill neonates and children. This begs the question: how will this demand be met?

Currently, the majority of pediatric bronchoscopists are pulmonologists or otolaryngologists. Our data supports the need for pediatric intensivists to be trained in this procedure. Indeed, Kohelet *et al.*^[27] proposed that neonatologists be trained in bedside FFB, given the high incidence of respiratory pathology in the NICU^[27]. Finally, more outcomes-based research regarding FFB and its impact on morbidity and mortality is needed in the NICU and PICU. Well-designed prospective, randomized multi-center trials to investigate clinical outcomes including mortality, length of mechanical ventilation, and length of ICU and hospital stay are needed. Furthermore, unlike in adults, the use of interventional FFB for procedures such as endobronchial stents, airway laser procedures, and endobronchial or transbronchial lung biopsies has received limited investigation in the pediatric population^[32]. Further studies of the safety and efficacy of interventional FFB could have significant impact in reducing open surgical procedures in children.

Our study identified indications, as well as diagnostic and therapeutic utility for FFB in critically ill children. In this review, FFB was associated with very few complications. This study provides the foundation for guidelines for FFB in critically ill children. Randomized studies are needed to investigate the impact of FFB on clinical outcomes.

COMMENTS

Background

Flexible fiberoptic bronchoscopy (FFB) is used with increasing frequency in neonatal and pediatric populations. However, there are no recent guidelines regarding its use in these populations.

Research frontiers

The indications for use of FFB in critically ill children are not well delineated. Understanding the diagnostic yield, therapeutic efficacy, and rate of adverse events related to FFB in critically ill children will help determine the indications for use of FFB in critically ill children.

Innovations and breakthroughs

FFB led to a change in medical management in 28.9% of critically ill children, with a diagnostic yield of 82%. Bronchoalveolar lavage obtained during FFB may assist with identifying infectious organisms (25.7%) and optimizing antimicrobial therapy (19.1%). FFB had therapeutic benefit with removal of mucus plugs or resolution of atelectasis in 60.3%. The majority of reported adverse events were transient and included hypotension, hypoxia and/or bradycardia requiring minimal intervention.

Applications

FFB is effective and safe for diagnostic and therapeutic use among critically ill pediatric patients. In particular, FFB is recommended in patients with upper airway symptoms (e.g., stridor), in immunocompromised patients with respiratory distress, and in immunocompetent patients with respiratory distress in addition to fever and/or persistent infiltrates on chest X-ray.

Terminology

FFB is a procedure that allows visualization of the upper and lower airways using a flexible bronchoscope. FFB can also be used to remove fluid or mucous plugs from the airways. Bronchoalveolar lavage is a procedure where fluid is squirted through the bronchoscope into the lungs and then recollected in order to diagnose lung disease.

Peer-review

A well written paper with good research of English literature.

REFERENCES

- 1 **Wood RE**, Fink RJ. Applications of flexible fiberoptic bronchoscopes in infants and children. *Chest* 1978; **73**: 737-740 [PMID: 639589 DOI: 10.1378/chest.73.5_Supplement.737]
- 2 **Barbato A**, Magarotto M, Crivellaro M, Novello A, Cracco A, de Blic J, Scheinmann P, Warner JO, Zach M. Use of the paediatric bronchoscope, flexible and rigid, in 51 European centres. *Eur Respir J* 1997; **10**: 1761-1766 [PMID: 9272916 DOI: 10.1183/09031936.97.10081761]
- 3 **Tang LF**, Chen ZM. Fiberoptic bronchoscopy in neonatal and pediatric intensive care units: a 5-year experience. *Med Princ Pract* 2009; **18**: 305-309 [PMID: 19494539 DOI: 10.1159/000215729]
- 4 **de Blic J**, Delacourt C, Scheinmann P. Ultrathin flexible bronchoscopy in neonatal intensive care units. *Arch Dis Child* 1991; **66**: 1383-1385 [PMID: 1776881 DOI: 10.1136/adc.66.12.1383]
- 5 **Nakano T**, Shikada M, Nomura M, Kuwayama-Komaki F, Suganuma E, Ishikawa-Kato M, Sakai T, Hirakawa H, Ueno S, Yokoyama S, Niimura F, Oh Y. Feasibility of fiberoptic bronchoscopy for small infants including newborns. *Tokai J Exp Clin Med* 2004; **29**: 1-5 [PMID: 15449805]
- 6 **Ernst A**, Silvestri GA, Johnstone D. Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. *Chest* 2003; **123**: 1693-1717 [PMID: 12740291 DOI: 10.1378/chest.123.5.1693]
- 7 Guidelines for fiberoptic bronchoscopy in adults. American Thoracic Society. Medical Section of the American Lung Association. *Am Rev Respir Dis* 1987; **136**: 1066 [PMID: 3662229 DOI: 10.1164/ajrccm/136.4.1066]
- 8 **Du Rand IA**, Blakley J, Booton R, Chaudhuri N, Gupta V, Khalid S, Mandal S, Martin J, Mills J, Navani N, Rahman NM, Wrightson JM, Munavvar M. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax* 2013; **68** Suppl 1: i1-i44 [PMID: 23860341 DOI: 10.1136/thoraxjnl-2013-203618]
- 9 **Green CG**, Eisenberg J, Leong A, Nathanson I, Schnapf BM, Wood RE. Flexible endoscopy of the pediatric airway. *Am Rev Respir Dis* 1992; **145**: 233-235 [PMID: 1731588 DOI: 10.1164/ajrccm/145.1.233]
- 10 **Midulla F**, de Blic J, Barbato A, Bush A, Eber E, Kotecha S, Haxby E, Moretti C, Pohunek P, Ratjen F. Flexible endoscopy of paediatric airways. *Eur Respir J* 2003; **22**: 698-708 [PMID: 14582925 DOI: 10.1183/09031936.02.00113202]
- 11 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]
- 12 **PROSPERO**. International prospective register of systematic reviews [Accessed 2014 September]. Available from: URL: <http://www.crd.york.ac.uk/PROSPERO/>
- 13 **Trikalinos TA**, Trow P, Schmid CH. Simulation-Based Comparison of Methods for Meta-Analysis of Proportions and Rates [Internet]. Available from: URL: <http://www.ncbi.nlm.nih.gov/pubmed/?term=24404633>
- 14 **Atzori P**, Iacobelli BD, Bottero S, Spiridakis J, Laviani R, Trucchi A, Braguglia A, Bagolan P. Preoperative tracheobronchoscopy in newborns with esophageal atresia: does it matter? *J Pediatr Surg* 2006; **41**: 1054-1057 [PMID: 16769333 DOI: 10.1016/j.jpedsurg.2006.01.074]
- 15 **Ward RF**, Arnold JE, Healy GB. Flexible minibronchoscopy in children. *Ann Otol Rhinol Laryngol* 1987; **96**: 645-649 [PMID: 3688750 DOI: 10.1177/000348948709600605]
- 16 **Efrati O**, Sadeh-Gornik U, Modan-Moses D, Barak A, Szeinberg A, Vardi A, Paret G, Toren A, Vilozni D, Yahav Y. Flexible bronchoscopy and bronchoalveolar lavage in pediatric patients with lung disease. *Pediatr Crit Care Med* 2009; **10**: 80-84 [PMID: 19057431 DOI: 10.1097/PCC.0b013e31819372ea]
- 17 **Davidson MG**, Coutts J, Bell G. Flexible bronchoscopy in pediatric intensive care. *Pediatr Pulmonol* 2008; **43**: 1188-1192 [PMID: 19009620 DOI: 10.1002/ppul.20910]
- 18 **Chapotte C**, Monrignal JP, Pezard P, Jeudy C, Subayi JB, De Brux JL, Cottineau C, Granry JC. Airway compression in children due to congenital heart disease: value of flexible fiberoptic bronchoscopic assessment. *J Cardiothorac Vasc Anesth* 1998; **12**: 145-152 [PMID: 9583543 DOI: 10.1016/s1053-0770(98)90321-4]
- 19 **Kamat PP**, Popler J, Davis J, Leong T, Piland SC, Simon D, Harsch A, Teague WG, Fortenberry JD. Use of flexible bronchoscopy in pediatric patients receiving extracorporeal membrane oxygenation (ECMO) support. *Pediatr Pulmonol* 2011; **46**: 1108-1113 [PMID: 21815274 DOI: 10.1002/ppul.21480]
- 20 **Manna SS**, Durward A, Moganasundram S, Tibby SM, Murdoch IA. Retrospective evaluation of a paediatric intensivist-led flexible bronchoscopy service. *Intensive Care Med* 2006; **32**: 2026-2033 [PMID: 16941167 DOI: 10.1007/s00134-006-0351-y]
- 21 **Nayak PP**, Sheth J, Cox PN, Davidson L, Forte V, Manliot C, McCrindle BW, Schwartz SM, Solomon M, Van Arsdell GS, Sivarajan VB. Predictive value of bronchoscopy after infant cardiac surgery: a prospective study. *Intensive Care Med* 2012; **38**: 1851-1857 [PMID: 23011533 DOI: 10.1007/s00134-012-2702-1]
- 22 **Hintz SR**, Sheehan AM, Halamek LP, Rhine WD, Van Meurs KP, Benitz WE, Frankel LR. Use of bronchoscopy for congenital diaphragmatic hernia patients on extracorporeal membrane oxygenation. *Clin Intens Care* 2002; **13**: 103-108 [DOI: 10.1080/714028795]
- 23 **Prentice E**, Mastropietro CW. Flexible bronchoscopy for children on extracorporeal membrane oxygenation for cardiac failure. *Pediatr Crit Care Med* 2011; **12**: 422-425 [PMID: 21057355 DOI: 10.1097/PCC.0b013e3181fe3010]
- 24 **Bar-Zohar D**, Sivan Y. The yield of flexible fiberoptic bronchoscopy in pediatric intensive care patients. *Chest* 2004; **126**: 1353-1359 [PMID: 15486403 DOI: 10.1378/chest.126.4.1353]
- 25 **Abu-Kishk I**, Klin B, Eshel G. Hemoptysis in children: a single institutional experience. *Pediatr Emerg Care* 2012; **28**: 1206-1210 [PMID: 23114250 DOI: 10.1097/PEC.0b013e318271c107]
- 26 **Fan LL**, Sparks LM, Fix FJ. Flexible fiberoptic endoscopy for airway problems in a pediatric intensive care unit. *Chest* 1988; **93**: 556-560 [PMID: 3342665 DOI: 10.1378/chest.93.3.556]
- 27 **Kohelet D**, Arbel E, Shinwell ES. Flexible fiberoptic bronchoscopy—a bedside technique for neonatologists. *J Matern Fetal Neonatal Med* 2011; **24**: 531-535 [PMID: 20617894 DOI: 10.3109/14767058.2010.501123]
- 28 **Kolat T**, Aunganon K, Yosthiem P. Airway complications in neonates who received mechanical ventilation. *J Med Assoc Thai* 2002; **85** Suppl 2: S455-S462 [PMID: 12403220]
- 29 **Kotby AA**, Shaheen MA, Basim HH, El Masry AA, Mansour MG, Abdel Fattah MA. Diagnostic bronchoalveolar lavage (BAL) for pulmonary fungal infections in critically ill children. *J Bronchology* 2008; **15**: 4-10 [DOI: 10.1097/LBR.0b013e3181608662]
- 30 **Myer CM**, Thompson RF. Flexible fiberoptic bronchoscopy in the neonatal intensive care unit. *Int J Pediatr Otorhinolaryngol* 1988; **15**: 143-147 [PMID: 3397233 DOI: 10.1016/0165-5876(88)90065-1]
- 31 **Nussbaum E**. Pediatric fiberoptic bronchoscopy: Clinical experience with 2,836 bronchoscopies. *Pediatr Crit Care Med* 2002; **3**: 171-176 [PMID: 12780989 DOI: 10.1177/000992289503400806]
- 32 **Peng YY**, Soong WJ, Lee YS, Tsao PC, Yang CF, Jeng MJ. Flexible bronchoscopy as a valuable diagnostic and therapeutic tool in pediatric intensive care patients: a report on 5 years of experience. *Pediatr Pulmonol* 2011; **46**: 1031-1037 [PMID: 21626712 DOI: 10.1002/ppul.21464]
- 33 **Soong WJ**, Jeng MJ, Hwang B. The application of a modified mini-flexible-fiberoptic endoscopy in pediatric practice. *Zhonghua Yixue Zazhi* (Taipei) 1995; **56**: 338-344 [PMID: 8605649]
- 34 **de Blic J**, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. *Eur Respir J* 2002; **20**: 1271-1276 [PMID: 12449184 DOI: 10.1183/09031936.02.02072001]
- 35 **Sachdev A**, Chugh K, Sethi M, Gupta D, Wattal C, Menon G. Diagnosis of ventilator-associated pneumonia in children in resource-limited setting: a comparative study of bronchoscopic and non-bronchoscopic methods. *Pediatr Crit Care Med* 2010; **11**: 258-266 [PMID: 19770785 DOI: 10.1097/PCC.0b013e3181bc5b00]
- 36 **Maggi JC**, Nussbaum E, Babbitt C, Maggi FE, Randhawa I. Pediatric fiberoptic bronchoscopy as adjunctive therapy in acute asthma

- with respiratory failure. *Pediatr Pulmonol* 2012; **47**: 1180-1184 [PMID: 22588986 DOI: 10.1002/ppul.22591]
- 37 **Pietsch JB**, Nagaraj HS, Groff DB, Yacoub UA, Roberts JL. Necrotizing tracheobronchitis: a new indication for emergency bronchoscopy in the neonate. *J Pediatr Surg* 1985; **20**: 391-393 [PMID: 4045664 DOI: 10.1016/s0022-3468(85)80225-6]
 - 38 **Olopade CO**, Prakash UB. Bronchoscopy in the critical-care unit. *Mayo Clin Proc* 1989; **64**: 1255-1263 [PMID: 2687588 DOI: 10.1016/s0025-6196(12)61288-9]
 - 39 **Joos L**, Patuto N, Chhajed PN, Tamm M. Diagnostic yield of flexible bronchoscopy in current clinical practice. *Swiss Med Wkly* 2006; **136**: 155-159 [PMID: 16633961]
 - 40 **Haenel JB**, Moore FA, Moore EE, Read RA. Efficacy of selective intrabronchial air insufflation in acute lobar collapse. *Am J Surg* 1992; **164**: 501-505 [PMID: 1443377 DOI: 10.1016/s0002-9610(05)81189-4]
 - 41 **Turner JS**, Willcox PA, Hayhurst MD, Potgieter PD. Fiberoptic bronchoscopy in the intensive care unit--a prospective study of 147 procedures in 107 patients. *Crit Care Med* 1994; **22**: 259-264 [PMID: 8306685 DOI: 10.1097/00003246-199402000-00017]
 - 42 **Paden ML**, Rycus PT, Thiagarajan RR. Update and outcomes in extracorporeal life support. *Semin Perinatol* 2014; **38**: 65-70 [PMID: 24580761 DOI: 10.1053/j.semperi.2013.11.002]
 - 43 **Soong WJ**, Jeng MJ, Lee YS, Tsao PC, Yang CF, Soong YH. Pediatric obstructive fibrinous tracheal pseudomembrane--characteristics and management with flexible bronchoscopy. *Int J Pediatr Otorhinolaryngol* 2011; **75**: 1005-1009 [PMID: 21640393 DOI: 10.1016/j.ijporl.2011.04.020]

P- Reviewer: Gow KW, Sinha R, Watanabe T **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL



Thoracic epidural anesthesia: Effects on splanchnic circulation and implications in Anesthesia and Intensive care

Antonio Siniscalchi, Lorenzo Gamberini, Cristiana Laici, Tommaso Bardi, Stefano Faenza

Antonio Siniscalchi, Lorenzo Gamberini, Cristiana Laici, Tommaso Bardi, Stefano Faenza, Division of Anesthesiology, Alma Mater Studiorum University of Bologna, 40138 Bologna, Italy

Author contributions: Siniscalchi A, Gamberini L, Laici C, Bardi T and Faenza S contributed to this manuscript.

Supported by The Department of Anesthesiology of the University of Bologna.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Antonio Siniscalchi, MD, Division of Anesthesiology, Alma Mater Studiorum University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. sinianest@libero.it
Telephone: +39-05-16363440

Received: August 27, 2014

Peer-review started: August 31, 2014

First decision: October 14, 2014

Revised: October 21, 2014

Accepted: November 17, 2014

Article in press: November 19, 2014

Published online: February 4, 2015

Function Tests. EMBASE, Cochrane library, ClinicalTrials.gov and clinicaltrialsregister.eu were also searched using the same terms.

RESULTS: Twenty-seven relevant studies and four ongoing trials were found. The data regarding the effects of epidural anesthesia on splanchnic perfusion are conflicting. The studies focusing on regional macro-hemodynamics in healthy animals and humans undergoing elective surgery, demonstrated no influence or worsening of regional perfusion in patients receiving thoracic epidural anesthesia (TEA). On the other hand most of the studies focusing on micro-hemodynamics, especially in pathologic low flow conditions, suggested that TEA could foster microcirculation.

CONCLUSION: The available studies in this field are heterogeneous and the results conflicting, thus it is difficult to draw decisive conclusions. However there is increasing evidence deriving from animal studies, that thoracic epidural blockade could have an important role in modifying tissue microperfusion and protecting microcirculatory weak units from ischemic damage, regardless of the effects on macro-hemodynamics.

Key words: Anesthesia; Epidural; Circulation; Splanchnic; Intestine; Microcirculation; Pancreatitis; Liver function tests

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Abstract

AIM: To evaluate the currently available evidence on thoracic epidural anesthesia effects on splanchnic macro and microcirculation, in physiologic and pathologic conditions.

METHODS: A PubMed search was conducted using the MeSH database. Anesthesia, Epidural was always the first MeSH heading and was combined by boolean operator AND with the following headings: Circulation, Splanchnic; Intestines; Pancreas and Pancreatitis; Liver

Core tip: Effects of thoracic epidural anesthesia on splanchnic circulation are still poorly understood. The influence on macro-hemodynamics seems to vary based on the metameric extension of the blockade, the volume repletion and the hemodynamic status of the patient. Thus epidural anesthesia could reduce regional blood flow to splanchnic organs and have detrimental effects on oxygen delivery. However, there is increasing

evidence, in particular deriving from animal studies, of a possible protective effect on microcirculation of the epidural blockade, especially in low flow states. In fact, despite reducing perfusion pressure, thoracic epidural anesthesia could foster perfusion of microcirculatory weak units and reduce local dysoxia.

Siniscalchi A, Gamberini L, Laici C, Bardi T, Faenza S. Thoracic epidural anesthesia: Effects on splanchnic circulation and implications in Anesthesia and Intensive care. *World J Crit Care Med* 2015; 4(1): 89-104 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i1/89.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i1.89>

INTRODUCTION

Thoracic epidural anesthesia is a widely used anesthetic technique providing excellent intra and postoperative analgesia. In recent years there have been efforts to further understand the effects of the sympathetic blockade this technique produces, in particular on the vascular perfusion. These effects may have a role in protecting the intestinal mucosa from injury, and promoting tissue healing, both in surgery and in pathologic scenarios such as acute pancreatitis. However, the mechanisms of organ protection and splanchnic hemodynamic effects of epidural anesthesia are not entirely clear yet, and the available evidence is conflicting.

Aims of the review

This systematic review intends to evaluate the currently available evidence on the effects of thoracic epidural anesthesia on the splanchnic macro and microcirculation, in physiologic and pathologic conditions. Animal and human studies were taken into consideration.

MATERIALS AND METHODS

A PubMed search was conducted using the MeSH database. "Anesthesia, Epidural" was always the first MeSH heading and was combined by boolean operator and with the following headings: Circulation, Splanchnic; Intestines; Liver Function Tests; Pancreas; Pancreatitis.

EMBASE and Cochrane library were also searched using the same terms.

Finally ClinicalTrials.gov and clinicaltrialsregister.eu was also searched using the term "epidural anesthesia".

The abstracts were reviewed by three independent researchers and those not relevant to the search were excluded, only English language articles were taken into consideration. The quality of the studies was assessed using the Delphi List^[1].

RESULTS

The search in Pubmed, EMBASE and Cochrane library produced a total of 245 results. Based on the review of the abstracts 219 were found not to be relevant and excluded. The full papers of the remaining 26 articles were independently reviewed by 3 researchers (Figure 1).

The Clinicaltrials.gov search produced a total of 420 studies, only 4 of these were relevant to our review. None of the trials found in clinicalregister.eu were relevant to the search terms (Figure 1).

Effects of epidural anesthesia on splanchnic circulation

The literature research found 26 studies related to splanchnic circulation, of these 17 were animal and 9 human studies.

Animal studies: Animal studies evaluating splanchnic regional macro-hemodynamics are synthesized in Table 1.

Three studies^[2-4] used centrally injected radioactive or colored microspheres to determine cardiac output and regional blood flow. The regional flow could be estimated by measuring organ or regional arterial blood samples radioactivity, or by microscopy after autopsies.

Sivarajan *et al*^[2] evaluated the effects of low (T10) and high (T1) epidural anesthesia on systemic hemodynamics and regional blood flow in anesthetized monkeys. The main findings of this study were that both CO and arterial blood pressure significantly decreased in both groups and more significantly in the high epidural T1 group. Low level epidural blockade did not significantly change absolute blood flow in splanchnic organs, while high blockade produced a significant reduction in hepatic blood flow.

Schäper *et al*^[3] studied the influence of a continuous epidural lidocaine infusion in animal models of endotoxemia, induced by continuous *i.v.* infusion of *Escherichia Coli* lipopolysaccharide (LPS). The result showed that blood flow to the gastrointestinal organs (stomach and ileum) was significantly higher in the epidural group despite a lower Mean arterial pressure (MAP). Hepatic blood flow initially decreased after the onset of the epidural blockade, but was comparable to the one in control groups in the course of LPS infusion. Finally the decrease in pH and base excess induced by endotoxemia was partially blunted by epidural blockade.

Meissner *et al*^[4] evaluated the effects of a thoracic epidural block on splanchnic blood flow in either awake or anesthetized dogs. No difference was found between the two groups, only an increase in liver perfusion when propofol was used as anesthetic agent.

Vagts *et al*^[5] evaluated the effects of volume

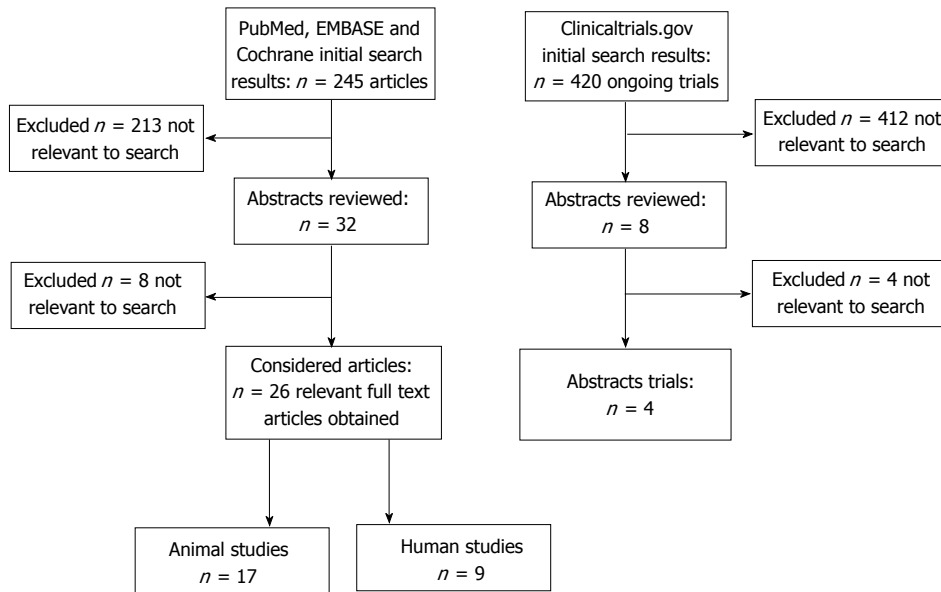


Figure 1 Flow chart showing selection of studies.

loading on hepatic perfusion in animals undergoing surgery with blended anesthesia. The hepatic flow measurement was obtained using perivascular flow-probes around the hepatic artery and portal vein; liver tissue PO_2 , plasma disappearance rate of indocyanine green (PDR_{ICG}), total hepatic DO_2 and VO_2 were also recorded. The main finding of this study was that the reduction in MAP induced by thoracic epidural blockade, was not associated with a decrease in total hepatic blood flow, DO_2 and parenchymal PO_2 . Volume loading could not modify macrohemodynamic parameters but significantly reduced portal venous oxygen content.

Ai *et al.*^[6] considered an animal model of systemic hypoxemia, finding that epidural blockade produced higher intramucosal and arterial pH, lower portal endotoxin and lower arterial lactate levels when compared to a control group. Portal blood flow remained stable during progressive hypoxia and was unaffected by epidural blockade.

Animal studies evaluating intestinal and pancreatic microhemodynamics are synthesized in Table 2.

Hogan *et al.*^[7,8], in two studies on rabbits, measured sympathetic efferent nerve activity, through surgically implanted electrodes in a postganglionic splanchnic nerve, and *in vivo* mesenteric vein diameter, to estimate venous capacitance.

The first protocol^[7] compared the effects of a thoraco-lumbar epidural block using different lidocaine concentrations (T2-L5), with injection of i.m. lidocaine. The results showed a reduction in sympathetic efferent nerve activity, and an increase in mesenteric vein diameter in animals treated with epidural lidocaine.

The second study^[8] investigated the different effects of a Thoracic (T4-L1) Thoracolumbar (T1-L4) and Lumbar (T11-L7) epidural block. The results

showed that Thoracic and Thoracolumbar blocks reduced sympathetic tone and increased mesenteric vein diameter, whilst a lumbar block produced opposite effects.

Kosugi *et al.*^[9] investigated the effect of epidural analgesia on intestinal macro and micro-hemodynamics and the alterations in gut barrier function elicited by continuous endotoxin infusion in rabbits. The histopathological evaluation of the intestinal mucosa samples, showed that epidural anesthesia reduced injury. Moreover higher intramucosal pH, and reduced mucosal permeability, were recorded in animals treated with thoracic epidural blockade, despite a decrease in perfusion pressure and arterial oxygen content.

Intravital microscopy of the ileus was used as an indirect measure of splanchnic flow in 5 studies^[10-14].

Sielenkämper *et al.*^[10] found, in anesthetized rats treated with epidural bupivacaine, an increase in arteriolar red blood cell velocity, expressing an increase in gut mucosal blood flow despite a lower MAP. Also, intercapillary area calculated for continuously perfused capillaries, was reduced in the TEA group, indicating a decrease in intermittent blood flow in the villus microcirculation.

Adolphs *et al.*^[11,12] investigated the effect of thoracic epidural anesthesia in hemorrhagic hypotension and normotensive endotoxemia in rats.

In the hemorrhagic hypotension model^[12], the pH and base excess, and muscularis layer capillary perfusion, were significantly improved in the group receiving epidural anesthesia. Moreover, leukocyte rolling after resuscitation was attenuated in thoracic epidural anesthesia (TEA) group, indicating a reduction in postischemic tissue injury.

In the normotensive endotoxemia model^[11], despite a lower MAP and an overall decrease in

Table 1 Animal studies evaluating macrohemodynamics and liver microhemodynamics

Subjects	Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Monkeys	Sivarajan <i>et al</i> ^[2]	1976	Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey	Prospective randomized	Anesthetized animals, epidural catheter placed L1-L2	9 (4 low epidural anesthesia - level T10 <i>vs</i> 5 high epidural anesthesia - level T1)	higher level T10 or T1	Radioactive microspheres and direct invasive monitoring of cardiac output	Low epidural - no difference in blood flow to major organs, while T1 epidural ↓ blood flow to liver, pancreas and gut (hepatic artery, portal vein)
Dogs	Meissner <i>et al</i> ^[4]	1999	Limited upper thoracic epidural block and splanchnic perfusion in dogs	Prospective observational	Induction of upper thoracic epidural in awake and anesthetized dogs and measurements of splanchnic perfusion	13 (6 anesthetized, 7 no)	T1-T5	Coloured microspheres injected in the aorta and then collected from tissue samples after autopsy	High TEA had no effect on sympathetic activity and splanchnic blood flow, nor in the awake nor anesthetized state. Propofol anaesthesia increased liver perfusion
Rabbits	Ai <i>et al</i> ^[6]	2001	Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits	Prospective randomized	Progressive hypoxia in anesthetized animals	18 (9 TEA/ Lidocaine <i>vs</i> 9 TEA/NaCl 0.9%)	insertion point T12-L1 and 3-4 cm advancement	Portal blood flow, portal oxygen extraction ratio, portal pH, portal Lactate, intramucosal pH (pHi) of the ileum, portal endotoxin	pHi and pHart significantly higher and portal Endotoxin and Lactate significantly lower in TEA/Lido group. No differences in portal blood flow
Pigs	Vagts <i>et al</i> ^[5]	2003	The effects of thoracic epidural anesthesia on hepatic perfusion and oxygenation in healthy pigs during general anesthesia and surgical stress	Prospective randomized	Anesthetized and acutely instrumented pigs, assigned to 3 groups: control <i>vs</i> TEA plus basic fluid (BF) <i>vs</i> TEA plus VL	19 (3 CTRL; 8 TEA alone; 8 TEA + VL)	T5 to T12	Hepatic blood flow using ultrasonic transit-time perivascular flowprobes around the hepatic artery and portal vein; multiwire surface electrode placed onto the liver to measure tissue surface PO ₂ ; PDR-icg	Despite a decrease in MAP, TEA had no effect on total hepatic blood flow, liver DO ₂ and VO ₂ . Liver tissue PO ₂ did not decrease. Lactate uptake and PDR-icg remained unchanged. Volume loading did not show any benefit with regard to hepatic perfusion, oxygenation, and function
Rats	Shäper <i>et al</i> ^[3]	2010	TEA attenuates endotoxin induced impairment of gastro intestinal organ perfusion	Prospective randomized	Sepsis model through infusion of LPS, evaluation of regional flow at 30', 60', 120'	18 (9 TEA <i>vs</i> 9 sham)	T4-T11 (methilen blue spread)	Fluorescent microspheres withdrawal technique, then evaluation of microspheres in brain, heart, ileopsoas muscle, liver pancreas gut segments; determination plasma catecholamines	TEA ↑ blood flow to GIT organs under LPS effect

Studies evaluating liver micro hemodynamics

Rats	Freise <i>et al</i> ^[17]	2009	Hepatic effects of TEA in experimental severe acute pancreatitis	Prospective randomized blinded image analysis	Animal model of acute pancreatitis induced by taurocholate injection or sham lesion	28 (7 sham + sham, 7 sham + TEA, 7 pancreat + sham, 7 pancreat + TEA) an additional 22 animals were assigned to the three group to asses hepatic apoptosis	catheter tip placed T6	Intravital microscopy of liver left lobe, cell adhesion to sinusoid wall (rollers and stickers), apoptosis of cells by Fas-L pathway	TEA ↑ diameter of sinusoids in pancreatitis, TEA ↓ the number of parenchymal apoptotic cells in pancreatitis (Fas-L pathway), TEA does not have much influence in sham groups
Rats	Freise <i>et al</i> ^[18]	2009	TEA reduces sepsis related hepatic hyperperfusion and reduces leucocyte adhesion in septic rats	Prospective randomized blinded image analysis	Sepsis model induced with cecal ligation and perforation	24 (8 sham + sham, 8 sepsis + TEA); another 21 animals were assessed for liver failure and hemodynamics	catheter tip placed T6	Intravital microscopy of liver left lobe, cell adhesion to sinusoid and venules, serum transaminase activity, TNFα activity	TEA ↓ sinusoid dilation in sepsis by probably restoring hepatic arterial buffer response. TEA ↓ temporary adhesion to sinusoid wall but did not affect permanent adhesion. TEA did not affect transaminase or TNF activity. No differences in hemodynamics

↑: Increase; ↓: Decrease; VL: Volume loading; TEA: Thoracic epidural anesthesia; CTRL: Control; MAP: Mean arterial pressure; PDRICG: Plasma disappearance rate of Indocyanine Green; LPS: Lipopolysaccharide; GIT: Gastrointestinal tract; HR: Heart rate; PEEP: Positive end expiratory pressure; HES: Hydroxyethyl starch; PCO₂: Carbon dioxide partial pressure; LEA: Lumbar epidural anesthesia; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Animal studies evaluating intestinal and pancreatic microhemodynamics

Subjects	Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Rabbits	Hogan <i>et al</i> ^[7]	1993	Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits	Prospective randomized	Anesthetized animals receiving thoraco-lumbar epidural block with different anesthetic concentrations	32 (7 lidocaine 6 mg/kg <i>im</i> vs 5 lidocaine 15 mg/kg <i>im</i> vs 5 TEA lido 0.5% vs 8 TEA lido 1.0% vs 7 TEA lido 1.5%)	T2-L5	Mesenteric vein diameter, sympathetic efferent nerve activity (SENA) of post ganglionic splanchnic nerve	TEA ↑ splanchnic venous capacitance and ↓ SENA
Rabbits	Hogan <i>et al</i> ^[8]	1995	Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits	Prospective randomized	Anesthetized and non anesthetized animals receiving either a thoracic or lumbar block with special epidural catheters limiting anesthetic spread	26 (6 lidocaine 1% TEA vs 6 lido 1% LEA, vs 8 thoracolumbar anesthesia in spontaneous ventilation with lido 1% vs 6 thoracolumbar anesthesia with lido 1% in fully awake animals)	T11-L7 (LEA group), T4-L1 (TEA group), T1-L4 (thoracolumbar anesthesia)	Mesenteric vein diameter, sympathetic efferent nerve activity (SENA) of post ganglionic splanchnic nerve	↑ SENA and ↓ mesenteric vein diameter after lumbar epidural anesthesia while ↓ SENA and ↑ mesenteric vein diameter after thoracic epidural anesthesia
Rats	Sielenk-äpper <i>et al</i> ^[10]	2000	Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats	Prospective randomized	Anesthetized and mechanically ventilated rats that underwent laparotomy to obtain access to the ileum	19: 11 bupivacaine 0.4% (TEA); 8 normal saline (CTRL)	Catheter tip placed T7-T9	Intravital microscopy on the ileum mucosa	TEA ↑ gut mucosal blood flow and ↓ the extent of intermittent flow in the villus microcirculation
Rats	Adolphs <i>et al</i> ^[12]	2003	Thoracic epidural anesthesia attenuates hemorrhage-induced impairment of intestinal perfusion in rats	Prospective randomized	Hemorrhagic shock model (PAM 30 mmHg for 60 min) induced by withdrawal of blood and subsequent retransfusion for resuscitation	32 (4 groups of 8); epidural lidocaine 2% (TEA) or normal saline (CTRL), muscularis or mucosa evaluated	catheter tip placed T11-T12	Intravital microscopy with fluorescein (FCD = functional capillary density and erythrocyte velocity in the mucosa and muscularis of distal ileum)	TEA ↑ intestinal microvascular perfusion and ↓ hypotension-induced impairment of capillary perfusion in the muscularis, ↓ systemic acidemia during hypotension and ↓ leukocyte rolling after resuscitation

Rats	Adolphs <i>et al</i> ^[11]	2004	Effects of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia	Prospective randomized	Normotensive endotoxaemia model through LPS infusion in anesthetized animals	32 (8 no TEA vs 24 TEA) +/- <i>E.coli</i> LPS infusion +/- epidural lidocaine 2% or saline infusion, muscularis or mucosa evaluated	catheter tip placed T11-T12	Intravital microscopy with fluorescein (densities of perfused and non-perfused capillaries and erythrocyte velocity in both the mucosa and the muscularis of the terminal ileum)	TEA ↓ MAP and HR, ↑ muscularis and ↓ mucosal microvascular perfusion
Dogs	Schwarte <i>et al</i> ^[15]	2004	Effects of thoracic epidural anaesthesia on microvascular gastric mucosal oxygenation in physiological and compromised circulatory conditions in dogs	Prospective randomized	Chronically instrumented and anaesthetized dogs. Animals were studied under physiological and compromised circulatory conditions (PEEP 10 cm H ₂ O), both with and without fluid resuscitation	12 (6 lidocaine vs 6 saline)	catheter tip placed T10, thoracolumbar - paresis of the ocular nictitating membrane, sensory block up to the neck region, and motor block of the limbs	Gastric mucosal oxygenation by measuring microvascular haemoglobin oxygen saturation (μHbO ₂) using reflectance spectrophotometry	Under physiological conditions, TEA preserved gastric mucosal oxygenation but aggravated its reduction during impaired circulatory conditions, thereby preserving the correlation between gastric mucosal and systemic oxygenation. Fluid resuscitation completely restored these variables
Rabbits	Kosugi <i>et al</i> ^[9]	2005	Epidural analgesia prevents endotoxin-induced gut mucosal injury in rabbits	Prospective randomized	Normotensive endotoxaemia model through LPS infusion in anesthetized animals	PROTOCOL 1: 28 = 14 saline (C = CONTROL) vs 14 lidocaine (E = EPIDURAL); PROTOCOL 2: 20, into groups C or E (10 each group)	catheter placed via T11-T12 interspace	PROTOCOL 1: Measurements of systemic and splanchnic variables using catheter inserted through the mesenteric vein and perivascular probe attached around the portal vein. Intramucosal pH using tonometer catheter surgically inserted into the terminal ileum. Mucosal edema and microstructure of the terminal ileum using tissue sampling to determine wet-to-dry weight ratio and histological analysis (histopathological injury scores of gut mucosa). PROTOCOL 2: gut permeability using fluorescence spectrometry	The application of epidural analgesia in endotoxemic hosts attenuates the progression of intramucosal acidosis, the increase of intestinal permeability, and the structural alterations of intestinal villi, possibly through the restoration of microcirculation, despite a significant decrease of perfusion pressure and arterial oxygen content

Rats	Freise <i>et al</i> ^[13]	2006	Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis in rats	Prospective randomized	Animal model of acute pancreatitis (AP) induced by taurocholate injection or sham lesion	28 (4 groups of 7): sham + saline TEA (Sham) <i>vs</i> AP + saline TEA (PANC) <i>vs</i> AP + TEA (EPI) <i>vs</i> AP + delayed TEA (delayed EPI). Outcome protocol: (n = 30): 15 AP <i>vs</i> 15 TEA	catheter tip placed T6	Intravital microscopy of the ileal mucosa	TEA ↓ intercapillary area (↑ local perfusion) ↓ IL-6 and serum lactate and ↓ 66% mortality
Rats	Daudel <i>et al</i> ^[14]	2007	Continuous thoracic epidural anesthesia improves gut mucosal microcirculation in rats with sepsis	Prospective randomized, blinded image analysis	Sepsis model induced with cecal ligation and perforation (CLP)	27 (10 CLP/TEA <i>vs</i> 9 CLP/Control <i>vs</i> 8 sham laparotomy)	catheter tip placed T6	Intravital videomicroscopy performed on villi of ileum mucosa	Smaller intercapillary area hence ↑ villus perfusion in CLP/TEA <i>vs</i> CLP/Control. Diameter of terminal arterioles and red blood cell velocity didn't differ
Pigs	Bachmann <i>et al</i> ^[16]	2013	Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial	Prospective randomized	Animal model of SAP induced by intraductal injection of glycodeoxycholic acid in the main pancreatic duct followed by closure	34: 17 bupivacaine <i>via</i> TEA after induction of SAP (TEA) <i>vs</i> 17 no TEA (control)	catheter introduced T7-T8 and advanced 2 cm (documented by epidurogram)	Continuous measurement of the tissue oxygen tension (tpO ₂) using a flexible polarographic measuring probe placed in the pancreatic head and pancreatic microcirculation using Laser-Doppler imager during a period of 6 h after induction SAP. Histopathologic tissue damage (histopathologic severity score of acute pancreatitis) by postmortem examination of the animals sacrificed after 7 d of observation	TEA improved survival as well as pancreatic microcirculation and tissue oxygenation resulting in reduced histopathologic tissue-damage

↑: Increase; ↓: Decrease. TEA: Thoracic epidural anesthesia; LEA: Lumbar epidural anesthesia; SAP: Severe acute pancreatitis.

mucosal functional capillary density, epidural infusion of lidocaine reduced the non-perfused capillaries in the muscularis layer after 120 min of continuous LPS infusion. Moreover, erythrocyte velocity decreased in the mucosa and muscularis layer during endotoxemia, but was not influenced by epidural blockade.

Freise *et al*^[13] in a rodent model of acute pancreatitis, found a decrease in ileal mucosa intercapillary area, IL-6 and lactate levels, in animals treated with both immediate or delayed epidural injection of local anesthetic. These results indicate that a thoracic epidural block improved local perfusion. This group had also lower scores of pancreatic injury and a 66% decrease in mortality.

Daudel *et al*^[14] induced sepsis by cecal ligation and perforation in rats, finding a significant decrease in intercapillary area in the group treated with TEA,

without differences in terminal arterioles diameter and red blood cells velocity.

Schwarte *et al*^[15] evaluated the effects on gastric mucosal oxygenation of epidural anesthesia and volume loading, in either normal or compromised circulation, in dogs. Hemodynamic failure was induced with high PEEP levels.

In healthy animals, TEA induced a reduction in MAP and DO₂, preserving gastric mucosal oxygenation. In compromised circulatory conditions, TEA aggravated the reduction of gastric mucosal oxygenation; volume loading restored both DO₂ and mucosal oxygenation. TEA maintained a constant relationship between gastric mucosal and systemic oxygenation.

Bachmann *et al*^[16], evaluated a porcine model of acute pancreatitis finding that TEA enhanced

Table 3 Human studies

Ref.	Year	Title	Type of study	Scenario	No. subjects	Sensory blockade	Surrogate measure of splanchnic flow	Findings
Lundberg <i>et al</i> ^[19]	1990	Intestinal hemodynamics during laparotomy: effects of thoracic epidural anesthesia and dopamine in humans	Prospective observational	Patients undergoing abdominal aorto-bifemoral reconstruction	9	Catheter inserted T7-T8 or T8-T9 and advanced 2-3 cm	Superior mesenteric artery blood flow (SMABF) <i>via</i> electromagnetic flow probe, mesenteric arteriovenous oxygen difference mesenteric venous lactate	↓ SMABF and ↓ MAP only restored by dopamine infusion
Tanaka <i>et al</i> ^[23]	1997	The effect of dopamine on hepatic blood flow in patients undergoing epidural anesthesia	Prospective controlled	Patients ASA 1-2 undergoing elective gynecological surgery. Normotension maintained either with HES infusion or HES + dopamine	28 (7 no TEA <i>vs</i> 14 TEA + HES <i>vs</i> 7 TEA + HES + dopamine)	Upper T5	Hepatic blood flow using Plasma Disappearance Rate of indocyanine green (PDR-icg)	↓ PDR-icg in TEA + HES group, = PDR-icg in TEA + HES + dopamine group
Väisänen <i>et al</i> ^[25]	1998	Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery	Prospective randomized controlled	Patients undergoing elective aortic reconstruction surgery	20 (10 TEA <i>vs</i> 10 controls)	Catheter inserted T12-L1 and advanced 5 cm	Gastric and sigmoid mucosal PCO ₂ , pH _i . Splanchnic blood flow direct invasive measure by cannulation of hepatic vein and dye dilution method (indocyanine green)	No differences
Spackman <i>et al</i> ^[26]	2000	Effect of epidural blockade on indicators of splanchnic perfusion and gut function in critically ill patients with peritonitis: a randomised comparison of epidural bupivacaine with systemic morphine	Double-blinded, prospective, randomised, controlled	Critically ill patients admitted in ICU with peritonitis (and systemic sepsis) and adynamic small bowel following abdominal surgery	21 (10 intravenous morphine <i>vs</i> 11 epidural bupivacaine)	Low thoracic or high lumbar epidural catheter insertion	Gastric tonometry: gastric intramucosal pH (pH _{ig}) and the intramucosal-arterial PCO ₂ gradient (Pg-PaCO ₂)	Significant improvements in gastric mucosal perfusion (a rise in Pg-PaCO ₂ and a fall in pH _{ig} in the morphine group and a significant difference between groups in the Pg-PaCO ₂ trends) and in the ultrasound appearance of the small bowel in the epidural group
Gould <i>et al</i> ^[20]	2002	Effect of thoracic epidural anaesthesia on colonic blood flow	Prospective observational	Patients undergoing elective anterior resection for rectal cancer	15	Cahteter inserted T9-T10	Doppler flowmetry for inferior mesenteric artery flow and Laser Doppler flowmetry for serosal red cell flux	↓ inferior mesenteric artery flow and ↓ serosal red cell flux significantly correlated to ↓ MAP reverted only by vasoconstrictors usage
Michelet <i>et al</i> ^[22]	2007	Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy	Prospective controlled	Patients undergoing elective radical oesophagectomy, postoperative evaluation	27 (18 TEA <i>vs</i> 9 controls)	C8-T11	Gastric mucosal blood flow (GMBF) measured using laser Doppler flowmetry at 1 and 18 h post surgery	↑GMBF in TEA group without correlation with MAP or CI

Kortgen <i>et al</i> ^[27]	2009	Thoracic but not lumbar epidural anaesthesia increases liver blood flow after major abdominal surgery	Prospective	Patients undergoing major abdominal surgery	34 (17 TEA vs 17 LEA)	Thoracic catheters between T5-T6 and T9-T10, lumbar catheters between L1-L2 and L4-L5	Blood lactate levels, central venous oxygen saturation (ScvO ₂), PDR-icg	TEA but not LEA ↑ PDR-icg
Meierhenrich <i>et al</i> ^[21]	2009	The effects of thoracic epidural anesthesia on hepatic blood flow in patients under general anesthesia	Prospective controlled	Patients undergoing major pancreatic surgery	30 (15 TEA vs 5 TEA + Norepinephrine vs 10 no TEA)	T4-T11	Hepatic blood flow index and hepatic stroke volume index in the right and middle hepatic vein by use of multiplane TEE	↓ Hepatic venous blood flow. The combination of thoracic TEA with continuous infusion of NE seems to induce a further decrease in hepatic blood flow. CO was not affected by TEA
Trepnaitis <i>et al</i> ^[24]	2010	The influence of thoracic epidural anesthesia on liver hemodynamics in patients under general anesthesia	Prospective randomized	Patients undergoing upper abdominal surgery for carcinoma of the stomach, papilla of Vater, and pancreas	50 (40 TEA vs 10 controls)	T5-T12	Hepatic blood flow using Plasma Disappearance Rate of indocyanine green (PDR-icg)	↓ PDR-icg in TEA group, even if ephedrine was administered to correct hypotension. ↑ PDR-icg in patients receiving general anesthesia. CO was unaffected

↑: Increase; ↓: Decrease. HES: Hydroxyethyl starch; NE: Norepinephrine; TEA: Thoracic epidural anesthesia; TEE: Transesophageal echocardiography.

pancreatic microcirculation and oxygenation, and reduced histopathologic scores of tissue damage. Also, 7 d mortality was lower in animals treated with TEA.

Animal studies evaluating hepatic microhemodynamics are synthesized in Table 1.

Two studies by Freise *et al*^[17,18] used intravital microscopy to assess hepatic microcirculation in different pathologic animal models.

In acute pancreatitis in rats^[17], TEA prevented the vasoconstriction of sinusoids, but could not reduce the number of non perfused sinusoids. The number of parenchymal apoptotic cells was reduced by TEA, probably by inhibition of the Fas ligand pathway, without effects on leukocyte adhesion. In healthy animals, TEA did not exert any effect on the evaluated microcirculation parameters.

In a sepsis model induced by cecal ligation and perforation^[18], TEA was able to normalize the increase in blood flow to the liver and to decrease temporary leucocyte adhesion to the venular endothelium, but not the vasoconstriction of hepatic vasculature and temporary sinusoidal leukocyte adhesion, both induced by sepsis.

Human studies: Human studies are synthesized in Table 3.

Of the 9 human studies taken into consideration, 4 evaluated splanchnic hemodynamics by direct measures of blood flow, 5 measured derived parameters such as gastric tonometry, intramucosal

pH or PDR_{ICG}.

Three studies which used direct hemodynamic measures found a reduction in blood flow caused by TEA, even though different measuring techniques and different vessels were considered. One study showed that TEA improved microcirculatory parameters whilst worsening macro-hemodynamics.

Lundberg *et al*^[19] measured superior mesenteric artery blood flow *via* an electromagnetic flow probe. In this study TEA reduced vascular resistance and blood flow in the superior mesenteric artery, with no change in measured CO. These hemodynamic changes were successfully corrected by dopamine infusion.

Gould *et al*^[20] used doppler flowmetry to measure inferior mesenteric artery blood flow and laser doppler flowmetry to evaluate red cells flux. Results showed that TEA produced a reduction of blood flow and red cells flux in the inferior mesenteric artery, which was strictly correlated with the fall in MAP. The hemodynamic changes registered could be corrected by vasopressors infusion but not by goal directed fluid therapy.

Meierhenrich *et al*^[21] used transesophageal echography to estimate blood flow in the hepatic veins, finding a reduction in estimated liver blood flow after the induction of a thoracic epidural blockade. The reduction in blood flow was resistant to the correction of hypotension using vasopressors.

Michelet *et al*^[22] used doppler flowmetry to evaluate gastric mucosal blood flow in patients

Table 4 Delphi List for animal studies evaluating macrohemodynamics and liver microhemodynamics

	Hogan <i>et al</i> ^[7]	Hogan <i>et al</i> ^[8]	Sielenkämper <i>et al</i> ^[10]	Adolphs <i>et al</i> ^[12]	Adolphs <i>et al</i> ^[11]	Schwarte <i>et al</i> ^[15]	Kosugi <i>et al</i> ^[9]	Freise <i>et al</i> ^[13]	Daudel <i>et al</i> ^[14]	Bachmann <i>et al</i> ^[16]
Treatment allocation										
(1) Was a method of randomization performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria specified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the outcome assessor blinded?	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was the care provider blinded?	No	No	No	No	No	No	No	No	No	No
Was the patient blinded?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 5 Delphi list for animal studies evaluating gut and pancreatic microhemodynamics

	Lundberg <i>et al</i> ^[19]	Tanaka <i>et al</i> ^[23]	Väisänen <i>et al</i> ^[25]	Spackman <i>et al</i> ^[26]	Gould <i>et al</i> ^[20]	Michelet <i>et al</i> ^[22]	Kortgen <i>et al</i> ^[27]	Meierhenrich <i>et al</i> ^[21]	Trepénaitis <i>et al</i> ^[24]
Treatment allocation									
Was a method of randomization performed?	No	No	No	Yes	N/A	No	No	No	No
Was the treatment allocation concealed?	No	No	No	Yes	N/A	No	No	No	No
Were the groups similar at baseline regarding the most important prognostic indicators?	N/A	Yes	Don't know	Yes	N/A	Yes	No	Yes	Yes
Were the eligibility criteria specified?	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Was the outcome assessor blinded?	No	No	No	Yes	N/A	Don't know	Don't know	Yes	No
Was the care provider blinded?	No	No	No	No	N/A	No	No	No	No
Was the patient blinded?	No	Don't know	No	Yes	N/A	No	No	No	No
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 6 Delphi List for human studies

	Sivarajan <i>et al</i> ^[2]	Meissner <i>et al</i> ^[4]	Ai <i>et al</i> ^[6]	Vagts <i>et al</i> ^[5]	Shäper <i>et al</i> ^[3]	Freise <i>et al</i> ^[17]	Freise <i>et al</i> ^[18]
Treatment allocation							
Was a method of randomization performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	No	No	No	Yes	No	Yes	Yes
Were the groups similar at baseline regarding the most important prognostic indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria specified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Was the outcome assessor blinded?	No	No	don't know	No	Yes	Yes	Yes
Was the care provider blinded?	No	No	No	No	No	Yes	Yes
Was the patient blinded?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A

undergoing oesophagectomy. In this scenario TEA improved the microcirculatory perfusion of the gastric tube at 1 and 18 h after surgery, a result which did not correlate with the measured macro-

hemodynamic parameters.

The six studies using surrogate hemodynamic parameters had conflicting results. Tanaka *et al*^[23] used PDR-icg as indirect measure of hepatic blood

Table 7 Ongoing clinical trials

Title	Start year	Scenario	No. subjects	Current primary outcome measures	Current secondary outcome measures	Findings
Effect of Epidural Anesthesia on Pancreatic Perfusion and Clinical Outcome in Patients With Severe Acute Pancreatitis	July 2005	Acute pancreatitis with Ranson Criteria over 2, and/or CRP over 100, and or pancreatic necrosis on CT scan	35 (epidural anesthesia with carbostesin and fentanyl vs PCA with fentanyl)	Number of patients with adverse events related to epidural anesthesia, pancreatic perfusion measured by computerized tomography	Clinical outcome, Length of stay, admission to intensive care unit, need for surgery	n/d
Epidural Analgesia for Pancreatitis (EpiPan Study)	April 2014	Patients admitted to the ICU for acute pancreatitis	148 (PCEA with Ropivacaine and sufentanyl vs conventional analgesia - acetaminophen, nefopam, tramadol, opioids)	Ventilator-free days	Duration of invasive and/or non invasive mechanical ventilation, incidence of various complications, biological inflammatory response, cost analysis, incidence of intolerance to enteral feeding, effectiveness of pain management, duration of EA	n/d
Study of Effectiveness of Thoracic Epidural Analgesia for the Prevention of Acute Pancreatitis After ERCP Procedures	January 2008	Patients undergoing therapeutic ERCP for the first time without clinical signs of acute pancreatitis	491 (standard premedication + TEA vs standard premedication)	prevention of post-ERCP pancreatitis	Not provided	n/d
The Effects of Local Infiltration Versus Epidural Following Liver Resection 2 (LIVER 2)	December 2012	Patients undergoing open hepatic resection for benign or malignant conditions	100 (EA vs wound catheter)	Length of stay	Pain Scores, Molecular response to surgery, Central Venous Pressure, estimated Blood Loss, Operative field assessment, Pringle time, Quality of Life (EQ-5D), Morphine consumption, IV Fluid volume, Complications, Post-operative blood tests	n/d

flow, finding that TEA reduced blood flow to the liver, fluid resuscitation alone could not reverse this effect but had to be associated with dopamine infusion. Trepenaitis *et al*^[24] found a reduction of PDR_{ICG} in patients undergoing upper abdominal surgery with TEA. This data was not associated with a fall in CO and could not be reversed by administration of vasopressors.

Väisänen *et al*^[25] found no influence of TEA on gastric and sigmoidal PCO₂ gap in patients undergoing elective abdominal aortic surgery.

Spackman *et al*^[26] evaluated the effects of TEA on a group of critically ill patients with surgically treated peritonitis, they found better pHi and PCO₂ gap in patients treated with epidural infusion of bupivacaine.

Kortgen *et al*^[27] found an increase in liver blood flow measured with PDR_{ICG} in patients undergoing major abdominal surgery and treated with thoracic epidural anesthesia in addition to general anesthesia. This finding couldn't be replicated by using lumbar epidural anesthesia and general anesthesia as anesthetic technique.

The quality of animal and human studies assessed through Delphi List is synthesized in Tables

4-6.

The Animal studies considered in this review, in particular the most recent ones, are well designed; groups were homogeneous, methods were minutely described, and outcome assessors were frequently blinded. However, the high variability of surrogate measures used to estimate splanchnic blood flow in each study, is the biggest limit to the common interpretation of their results.

The quality of human studies was in general low. Most of the studies considered did not use randomization criteria, and the control groups were often composed by patients not eligible for epidural anesthesia, or who refused it. Patients were undergoing different surgical procedures, so that selection bias could not be excluded. Moreover, the outcome assessor was frequently not blinded. The outlined considerations limit the reliability of these studies, and underline the urgent need for well designed RCTs.

Ongoing clinical trials

Clinical trials search found 4 works of interest, which are synthesized in Table 7.

Two clinical trials are evaluating the effects of

thoracic epidural blockade on the clinical outcome of patients with acute pancreatitis.

One examines the hypothesis that thoracic epidural anesthesia for therapeutic ERCP could have a role in preventing post-ERCP pancreatitis.

Another study is comparing epidural anesthesia and the use of a wound catheter for post liver resection pain management. Amongst the secondary endpoints of this study are the molecular response to surgery, surgical and medical complications, and postoperative liver blood test results, which could all be modified by the microvascular effects of epidural blockade.

DISCUSSION

Splanchnic circulation and epidural blockade

Splanchnic blood flow is regulated by intrinsic and extrinsic mechanisms. Intrinsic factors include local myogenic and metabolic control, locally produced vasoactive substances and local reflexes. The main extrinsic factors are the sympathetic innervation and the circulating vasoactive substances.

Epidural blockade can interfere with all these factors, either by direct block of sympathetic efferents or by the systemic effects of circulating local anesthetics.

A thoracic epidural block influences the systemic hemodynamics by reducing the intestinal vascular resistance and the stimulation of the adrenal gland and the renin-angiotensin axis^[28].

The extension of the blockade seems to be a key factor in determining the splanchnic circulation response to epidural anesthesia. In fact the sympathetic innervation to the celiac, superior and inferior mesenteric ganglia originates in the T5-T11 region of the spinal cord, hence a low epidural block could not ensure a sufficient spread of local anesthetic to include all the efferent sympathetic innervation to the gut. Moreover the sympathetic activity in the regions not involved by the epidural blockade could be increased^[29]. For these reasons an epidural block limited to the upper thoracic region, could potentially result in splanchnic sympathetic hyperactivity and foster splanchnic ischemia. Meissner *et al.*^[4] tested this hypothesis and found no modifications in intestinal blood flow during epidural anesthesia extending to the T1-T5 metameres in dogs, indicating that other local or systemic mechanisms could counteract the sympathetic hyperactivity and maintain a normal blood flow.

The data available in current literature regarding the effects of thoracic epidural anesthesia on splanchnic perfusion are conflicting. Studies focusing on regional macro-hemodynamics in healthy animals^[2,5] and humans undergoing elective surgery^[19-21,23-25] demonstrated no influence or worsening of regional perfusion in subject receiving thoracic epidural

anesthesia. On the other hand most of the studies focusing on micro-hemodynamics^[7-12,17,18], especially those focusing on pathologic low flow conditions, suggested that TEA could foster microcirculation despite a reduction in mean perfusion pressure.

Intestinal microcirculation

The Gut receives its blood supply from three great vessels: the celiac artery, and the superior and inferior mesenteric arteries. The branchings of these three vessels result in a common set of mesenteric arteries evolving in two orders of arterioles, located in the superficial submucosa, forming a highly interconnected system to perfuse the small, third order arterioles.

Third order arterioles perfuse one or several villi, submucosal glands, crypt regions and the corresponding muscle layer, forming a mesh-like subepithelial capillary plexus. First and second order arterioles account for about 65% of the intestinal vascular resistance in rats, an additional 20% resistance resides in the capillaries and venules, so that terminal arterioles can govern only 15% of blood flow modifications^[30]. One or two veins drain each villus. The parallel arrangement of these vessels produces a countercurrent mechanism that is the basis for the oxygen shunting phenomena that account for the extreme sensitivity of the apical region of the villi to hypoxia^[31].

In low flow states, ischemia/reperfusion injury to the intestinal mucosa could damage the intestinal barrier and promote bacterial migration.

Intestinal circulation in sepsis

In sepsis and septic shock, both micro and macro-hemodynamics undergo profound alterations. However, the restoration of normal global hemodynamic and oxygen derived variables is not necessarily correlated to a correction of tissue dysoxia. This condition of oxygen extraction deficit could be correlated to metabolic disturbances or to regional hypoxia.

Microvascular flow distribution becomes highly heterogeneous during sepsis and septic shock, microcirculatory weak units can become hypoxic while other units can be overperfused.

These alterations are probably related to the presence of inflammatory mediators and micro-circulatory emboli that impair microvascular autoregulation and increase oxygen shunting. This explains the finding of a venous PO₂ higher than regional capillary PO₂ (PO₂ gap) in sepsis models^[32].

These observations are progressively changing the primary endpoint for resuscitation procedures: from global hemodynamic and oxygen derived variables, to microcirculatory oxygenation. In fact, administration of vasopressors, despite correcting macrohemodynamic and oxygen delivery, could have

counterproductive effects on microcirculation. This is the rationale for ongoing experimental therapies using vasodilators or oxygen carrying solutions to support dysoxic weak units^[33].

Thoracic epidural blockade applied to animal^[3,9,14] and human^[26] models of sepsis appeared to be effective in fostering microvascular circulation or at least modify its distribution^[11].

Regional sympathetic blockade could counteract the above mentioned mechanisms of heterogeneous flow distribution, restoring oxygenation to weak units, and thus contributing to the survival of the intestinal barrier^[9,34].

Intestinal circulation in non septic low flow states

In non septic low flow states, the correction of the hemodynamic status appears to restore oxygenation if a damage to the microcirculation has not developed yet.

Epidural anesthesia in this context could help maintaining microvascular perfusion, reducing ischemia/reperfusion injury and inflammation, as demonstrated by Adolphs *et al*^[12].

However, Schwarte *et al*^[15] found that TEA produced a reduction in gastric mucosal oxygenation in dog models of hemodynamic dysfunction induced by high PEEP levels. In this study the extension of the epidural block was thoraco-lumbar, which produced a significant fall in blood pressure compared to the control group. This was not the case in the study by Adolphs *et al*^[11], where hemodynamic disturbances were more limited. Overall TEA appears to have a protective role for intestinal microcirculation in hemorrhagic low flow states, until macro-hemodynamics are maintained.

Pancreatic microcirculation and acute pancreatitis

Pancreatic circulation is organized in a continuous network called insulo-acinar portal system. The pancreatic lobule is served by a single end artery, that first supplies blood to islets, and then continues as vasa efferentia to supply acini.

The autoregulation of this system is both hormonal and neural. The blood flow is strictly correlated to exocrine secretion, and modulated by various gastro-entero-pancreatic hormones.

This particular anatomy is very susceptible to ischemia, and it appears to have an important role in the development of acute pancreatitis^[35].

During acute pancreatitis, microvascular perfusion is altered in accordance to the severity of the disease^[36], and regional macro-hemodynamic blood flow appears not to correlate with microcirculation^[37]. Pancreatic blood flow, red cell velocity, and functional capillary density all decrease; end artery vasoconstriction and increased shunts lead to ischemia, necrosis and circulatory stasis^[38]. Moreover, local immune reaction and oxygen free radicals contribute to lobular and endothelial necrosis.

Animal models of acute pancreatitis treated with thoracic epidural blockade^[13,16], showed reduced histologic signs of pancreatic necrosis and a restoration of continuous capillary perfusion and arteriolar blood flow, moreover, survival rate was significantly higher in both of the studies.

The microcirculatory effects induced by TEA could contribute in interrupting the ischemic injury involved in the beginning and progression of pancreatic lesions.

Nowadays TEA is increasingly used in humans as an effective analgesic technique for acute pancreatitis and it appears to be safe^[39]. The currently ongoing clinical trials are expected to shed light on whether TEA can influence the prognosis of acute pancreatitis.

Liver circulation

Liver circulation is characterized by a double afferent flow from the portal vein and the hepatic artery. In physiologic conditions, the portal vein drains the digestive tract below the diaphragm, spleen, and pancreas and supplies approximately two thirds of the hepatic blood flow, whilst the hepatic artery supplies one third.

Regulation of this dual blood supply, is strictly regulated by the hepatic arterial buffer response (HABR). This mechanism is responsible for maintaining a constant total hepatic blood flow by adjusting the hepatic arterial flow in relation to the modifications of portal flow.

Mechanisms regulating HABR are not fully understood, adenosine seems to be an important mediator of hepatic artery resistance, and reduction in adenosine wash out consensual to a drop in portal blood flow could enhance arterial flow. However the mechanism appears to be more complex and other mediators could be involved^[40].

The studies evaluating the effects of TEA on liver macro hemodynamics in normal conditions, found no difference^[5], or a reduction^[2], in total hepatic blood flow. It must be noted that, when comparing the results of these two studies, the extension of epidural blockade could have influenced the outcome. In fact Vagts *et al*^[5] (cit) considered the effects of a T5-T12 block, while Sivarajan *et al*^[2] (cit) compared two levels of sensory blockade, finding a reduction of total hepatic blood flow only in the high level sensory blockade group (T1).

Liver circulation in sepsis

Total liver blood flow in sepsis and septic shock is usually increased, proportionally to the cardiac output^[41]. This is associated with a decreased oxygen hemoglobin saturation in the hepatic veins. The reasons behind these phenomena are probably an impairment of the HABR mechanism, and a mismatch between oxygen distribution and metabolic demand.

Microvascular circulation appears to be uncoupled from systemic circulation in this context. In fact, despite the hyperdynamic circulatory state, microvascular flow appears to be unchanged or even decreased^[42,43].

Intrahepatic blood flow is redistributed, blood is channeled away from contracted to dilated vessels reducing the perfused sinusoidal area. Imbalances in nitric oxide production may be the origin of these modifications. Moreover, sinusoidal and Kupffer cells are activated by contact with leukocytes and toxins, and react by producing cytokines which further impair microcirculation^[44,45].

The review of the literature found only one study^[18] considering the effect of epidural blockade on liver circulation in septic animals. In this scenario of late sepsis, TEA appeared to ameliorate sinusoidal hyperflow and reduce temporary venular leukocyte adhesion.

The authors suggested that TEA could have a role in restoring the impaired HABR, reducing the immune activation, through a direct reduction in hepatic sympathetic activity, which seems to have a role in the regulation of liver immunity. Also TEA, by fostering intestinal barrier function, would have an indirect role in preserving liver microcirculation and function.

The data obtained in the animal studies on acute pancreatitis also suggest a protective effect of TEA on liver circulation^[17]. In fact TEA prevented sinusoids constriction and reduced liver cells apoptosis.

In conclusion, epidural anesthesia has been increasingly used in the last decades as an effective analgesic technique. This method produces a central sympathetic blockade which has strong effects on macro and microcirculation, by reducing autonomic efference and modifying the endocrine profile.

In recent years there have been efforts to further understand the underlying mechanisms of this technique. The available studies to date are heterogeneous and show conflicting results, making it difficult to gather decisive conclusions. A recent review by Richards *et al.*^[46] investigated the effects of TEA on splanchnic blood flow, focusing in particular on its potential implications in abdominal surgery. Their analysis, which comprised some of the studies that have been taken into consideration in the present review, also found the results to be inconsistent when suggesting a protective or detrimental effect of TEA on splanchnic circulation.

Overall the studies we considered also suggest possible new therapeutic applications of TEA, especially if micro-hemodynamics are taken into consideration.

Thoracic epidural anesthesia appears to reduce regional blood flow in relation to its effects on the vascular resistance, but at the same time it seems to foster microcirculation, especially in pathologic

low flow states, or in conditions involving a degree of microvascular dysfunction. In these scenarios epidural anesthesia seems to restore blood flow to microcirculatory weak units, ameliorating tissue dysoxia and resistance to hypoperfusion.

However, given the variable extension that the epidural blockade can have, a wide extension of the blockade could impair macro-circulation enough to reduce regional DO₂ under tissue requirements thus worsening hypoxia.

Human studies mostly evaluated macro-hemodynamics in patients undergoing surgery. Currently ongoing clinical trials could identify interesting applications in the prevention and treatment of acute pancreatitis, which have been strongly suggested by animal studies.

Further studies should investigate: (1) what is the extension of epidural blockade and local anesthetic concentration which can grant better micro-perfusion without significant hemodynamic impairment; (2) the effects on mortality and risk of catheter infection in septic animals treated with epidural anesthesia; (3) the effect of epidural blockade on the perioperative splanchnic organs function tests to assess whether epidural anesthesia can reduce perioperative organ injury or whether its macro-hemodynamic effects are relevant in inducing organ injury; and (4) the effect of epidural anesthesia on hepatic arterial buffer response, given the fact that this mechanism appears to be implicated in the constriction of the hepatic artery and the hemodynamic alterations developing after a liver resection, which could have a role in promoting Small for Size Syndrome^[47].

COMMENTS

Background

Thoracic epidural anesthesia is a broadly used analgesic technique, however its eventual therapeutic effects in different fields are still matter of debate.

Research frontiers

Macro and microcirculatory effects that result from the interaction between the analgesic technique and the neuro-endocrine system are suggested to have some therapeutic effect in animal models, studies on humans are scanty and use different methods for measuring hemodynamic variables, hence a thorough comparison is difficult. The hotspot of this Systematic Review is to evaluate up to date literature considering macro and microcirculatory effects of thoracic epidural anesthesia on splanchnic circulation and their possible therapeutic implications.

Innovations and breakthroughs

This Review considered the peculiarities of each particular regional circulation of the abdominal organs in order to evaluate possible effects of thoracic epidural anesthesia in both physiologic and pathologic conditions, this could change the way we use this technique, making it glide into a more comprehensive therapeutic view of its usage in medical and surgical conditions.

Applications

This Review points out some research fields that would be of interest in everyday clinical practice. In fact, on the basis of some rodent models, it appears that epidural anesthesia could reduce the mortality of acute pancreatitis, so that it could be used as a simultaneously analgesic and therapeutic procedure for this pathology. Moreover it has profound effects on hepatic circulation that could influence the function of this organ when it is object of surgical interventions. At last, some interesting implications in abdominal sepsis conditions are discussed.

Peer-review

The study was well designed and carried out. The data and conclusions are convincing.

REFERENCES

- 1 **Verhagen AP**, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998; **51**: 1235-1241 [PMID: 10086815 DOI: 10.1016/S0895-4356(98)00131-0]
- 2 **Sivarajan M**, Amory DW, Lindbloom LE. Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey. *Anesthesiology* 1976; **45**: 300-310 [PMID: 822752 DOI: 10.1097/00000542-197609000-00010]
- 3 **Schäper J**, Ahmed R, Perschel FH, Schäfer M, Habazettl H, Welte M. Thoracic epidural anesthesia attenuates endotoxin-induced impairment of gastrointestinal organ perfusion. *Anesthesiology* 2010; **113**: 126-133 [PMID: 20526186 DOI: 10.1097/ALN.0b013e3181de0fdd]
- 4 **Meissner A**, Weber TP, Van Aken H, Rolf N. Limited upper thoracic epidural block and splanchnic perfusion in dogs. *Anesth Analg* 1999; **89**: 1378-1381 [PMID: 10589611]
- 5 **Vagts DA**, Iber T, Puccini M, Szabo B, Haberstroh J, Villinger F, Geiger K, Nöldge-Schomburg GF. The effects of thoracic epidural anesthesia on hepatic perfusion and oxygenation in healthy pigs during general anesthesia and surgical stress. *Anesth Analg* 2003; **97**: 1824-1832 [PMID: 14633568 DOI: 10.1213/01.ANE.0000087062.94268.C5]
- 6 **Ai K**, Kotake Y, Satoh T, Serita R, Takeda J, Morisaki H. Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits. *Anesthesiology* 2001; **94**: 263-269 [PMID: 11176091 DOI: 10.1097/00000542-200102000-00016]
- 7 **Hogan QH**, Stadnicka A, Stekiel TA, Bosnjak ZJ, Kampine JP. Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits. *Anesthesiology* 1993; **79**: 1250-1260 [PMID: 8267201 DOI: 10.1097/00000542-199312000-00016]
- 8 **Hogan QH**, Stekiel TA, Stadnicka A, Bosnjak ZJ, Kampine JP. Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. *Anesthesiology* 1995; **83**: 604-610 [PMID: 7661361 DOI: 10.1097/00000542-199509000-00020]
- 9 **Kosugi S**, Morisaki H, Satoh T, Ai K, Yamamoto M, Soejima J, Serita R, Kotake Y, Ishizaka A, Takeda J. Epidural analgesia prevents endotoxin-induced gut mucosal injury in rabbits. *Anesth Analg* 2005; **101**: 265-272, table of contents [PMID: 15976243]
- 10 **Sielenkämper A**, Brodner G, Van Aken H. Epidural anesthesia and splanchnic perfusion. *Can J Anaesth* 2001; **48**: 611-612 [PMID: 11444460 DOI: 10.1007/BF03016842]
- 11 **Adolphs J**, Schmidt DK, Korsukewitz I, Kamin B, Habazettl H, Schäfer M, Welte M. Effects of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia. *Intensive Care Med* 2004; **30**: 2094-2101 [PMID: 15338125 DOI: 10.1007/s00134-004-2426-y]
- 12 **Adolphs J**, Schmidt DK, Mousa SA, Kamin B, Korsukewitz I, Habazettl H, Schäfer M, Welte M. Thoracic epidural anesthesia attenuates hemorrhage-induced impairment of intestinal perfusion in rats. *Anesthesiology* 2003; **99**: 685-692 [PMID: 12960554 DOI: 10.1097/00000542-200309000-00025]
- 13 **Freise H**, Lauer S, Anthonen S, Hlouschek V, Minin E, Fischer LG, Lerch MM, Van Aken HK, Sielenkämper AW. Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis in rats. *Anesthesiology* 2006; **105**: 354-359 [PMID: 16871070 DOI: 10.1097/00000542-200608000-00019]
- 14 **Daudel F**, Freise H, Westphal M, Stubbe HD, Lauer S, Bone HG, Van Aken H, Sielenkämper AW. Continuous thoracic epidural anesthesia improves gut mucosal microcirculation in rats with sepsis. *Shock* 2007; **28**: 610-614 [PMID: 17589385]
- 15 **Schwarte LA**, Picker O, Höhne C, Fournell A, Scheeren TW. Effects of thoracic epidural anaesthesia on microvascular gastric mucosal oxygenation in physiological and compromised circulatory conditions in dogs. *Br J Anaesth* 2004; **93**: 552-559 [PMID: 15277300 DOI: 10.1093/bja/ae235]
- 16 **Bachmann KA**, Trepte CJ, Tomkötter L, Hinsch A, Stork J, Bergmann W, Heidelmann L, Strate T, Goetz AE, Reuter DA, Izbicki JR, Mann O. Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial. *Crit Care* 2013; **17**: R281 [PMID: 24314012 DOI: 10.1186/cc13142]
- 17 **Freise H**, Lauer S, Konietzny E, Hinkelmann J, Minin E, Van Aken HK, Lerch MM, Sielenkämper AW, Fischer LG. Hepatic effects of thoracic epidural analgesia in experimental severe acute pancreatitis. *Anesthesiology* 2009; **111**: 1249-1256 [PMID: 19934868 DOI: 10.1097/ALN.0b013e3181c1494e]
- 18 **Freise H**, Daudel F, Grosserichter C, Lauer S, Hinkelmann J, Van Aken HK, Sielenkämper AW, Westphal M, Fischer LG. Thoracic epidural anesthesia reverses sepsis-induced hepatic hyperperfusion and reduces leukocyte adhesion in septic rats. *Crit Care* 2009; **13**: R116 [PMID: 19594914 DOI: 10.1186/cc7965]
- 19 **Lundberg J**, Lundberg D, Norgren L, Ribbe E, Thörne J, Werner O. Intestinal hemodynamics during laparotomy: effects of thoracic epidural anesthesia and dopamine in humans. *Anesth Analg* 1990; **71**: 9-15 [PMID: 2194404 DOI: 10.1213/00000539-199007000-00002]
- 20 **Gould TH**, Grace K, Thorne G, Thomas M. Effect of thoracic epidural anaesthesia on colonic blood flow. *Br J Anaesth* 2002; **89**: 446-451 [PMID: 12402724 DOI: 10.1093/bja/89.3.446]
- 21 **Meierhenrich R**, Wagner F, Schütz W, Rockemann M, Steffen P, Senfleben U, Gauss A. The effects of thoracic epidural anesthesia on hepatic blood flow in patients under general anesthesia. *Anesth Analg* 2009; **108**: 1331-1337 [PMID: 19299808 DOI: 10.1213/ane.0b013e3181966e6f]
- 22 **Michalet P**, Roch A, D'Journo XB, Blayac D, Barrau K, Papazian L, Thomas P, Auffray JP. Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy. *Acta Anaesthesiol Scand* 2007; **51**: 587-594 [PMID: 17430321 DOI: 10.1111/j.1399-6576.2007.01290.x]
- 23 **Tanaka N**, Nagata N, Hamakawa T, Takasaki M. The effect of dopamine on hepatic blood flow in patients undergoing epidural anesthesia. *Anesth Analg* 1997; **85**: 286-290 [PMID: 9249101]
- 24 **Trepnaitis D**, Pundzius J, Macas A. The influence of thoracic epidural anesthesia on liver hemodynamics in patients under general anesthesia. *Medicina (Kaunas)* 2010; **46**: 465-471 [PMID: 20966619]
- 25 **Väisänen O**, Parviainen I, Ruokonen E, Hippeläinen M, Berg E, Hendolin H, Takala J. Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery. *Br J Anaesth* 1998; **81**: 893-898 [PMID: 10211015 DOI: 10.1093/bja/81.6.893]
- 26 **Spackman DR**, McLeod AD, Prineas SN, Leach RM, Reynolds F. Effect of epidural blockade on indicators of splanchnic perfusion and gut function in critically ill patients with peritonitis: a randomised comparison of epidural bupivacaine with systemic morphine. *Intensive Care Med* 2000; **26**: 1638-1645 [PMID: 11193270 DOI: 10.1007/s001340000671]
- 27 **Kortgen A**, Silomon M, Pape-Becker C, Buchinger H, Grundmann U, Bauer M. Thoracic but not lumbar epidural anaesthesia increases liver blood flow after major abdominal surgery. *Eur J Anaesthesiol* 2009; **26**: 111-116 [PMID: 19142083 DOI: 10.1097/EJA.0b013e32831c8939]
- 28 **Hopf HB**, Schlaghecke R, Peters J. Sympathetic neural blockade by thoracic epidural anesthesia suppresses renin release in response to arterial hypotension. *Anesthesiology* 1994; **80**: 992-99; discussion 992-99; [PMID: 8017664]
- 29 **Taniguchi M**, Kasaba T, Takasaki M. Epidural anesthesia enhances sympathetic nerve activity in the unanesthetized segments in cats. *Anesth Analg* 1997; **84**: 391-397 [PMID: 9024036]
- 30 **Bohlen HG**. Integration of intestinal structure, function, and microvascular regulation. *Microcirculation* 1998; **5**: 27-37 [PMID: 9702720 DOI: 10.1111/j.1549-8719.1998.tb00050.x]

- 31 **Vollmar B**, Menger MD. Intestinal ischemia/reperfusion: microcirculatory pathology and functional consequences. *Langenbecks Arch Surg* 2011; **396**: 13-29 [PMID: 21088974 DOI: 10.1007/s00423-010-0727-x]
- 32 **Ince C**, Sinaasappel M. Microcirculatory oxygenation and shunting in sepsis and shock. *Crit Care Med* 1999; **27**: 1369-1377 [PMID: 10446833 DOI: 10.1097/00003246-199907000-00031]
- 33 **Lamontagne F**, Meade M, Ondiveeran HK, Lesur O, Fox-Robichaud AE. Nitric oxide donors in sepsis: a systematic review of clinical and in vivo preclinical data. *Shock* 2008; **30**: 653-659 [PMID: 18497711 DOI: 10.1097/SHK.0b013e3181777eef]
- 34 **Schäper J**, Wagner A, Enigk F, Brell B, Mousa SA, Habazettl H, Schäfer M. Regional sympathetic blockade attenuates activation of intestinal macrophages and reduces gut barrier failure. *Anesthesiology* 2013; **118**: 134-142 [PMID: 23221864 DOI: 10.1097/ALN.0b013e3182784c93]
- 35 **Cuthbertson CM**, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg* 2006; **93**: 518-530 [PMID: 16607683 DOI: 10.1002/bjs.5316]
- 36 **Klar E**, Schratt W, Foitzik T, Buhr H, Herfarth C, Messmer K. Impact of microcirculatory flow pattern changes on the development of acute edematous and necrotizing pancreatitis in rabbit pancreas. *Dig Dis Sci* 1994; **39**: 2639-2644 [PMID: 7995190 DOI: 10.1007/BF02087702]
- 37 **Schröder T**, Kivisaari L, Standertskjöld-Nordenstam CG, Somer K, Lehtola A, Puolakkainen P, Karonen SL, Kivilaakso E, Lempinen M. Pancreatic blood flow and contrast enhancement in computed tomography during experimental pancreatitis. *Eur Surg Res* 1985; **17**: 286-291 [PMID: 4054186 DOI: 10.1159/000128480]
- 38 **Zhou ZG**, Chen YD. Influencing factors of pancreatic microcirculatory impairment in acute pancreatitis. *World J Gastroenterol* 2002; **8**: 406-412 [PMID: 12046059]
- 39 **Bernhardt A**, Kortgen A, Niesel HCh, Goertz A. Using epidural anesthesia in patients with acute pancreatitis--prospective study of 121 patients. *Anaesthesiol Reanim* 2002; **27**: 16-22 [PMID: 11908096]
- 40 **Jakob SM**. Splanchnic blood flow in low-flow states. *Anesth Analg* 2003; **96**: 1129-1138, table of contents [PMID: 12651672]
- 41 **Asfar P**, De Backer D, Meier-Hellmann A, Radermacher P, Sakka SG. Clinical review: influence of vasoactive and other therapies on intestinal and hepatic circulations in patients with septic shock. *Crit Care* 2004; **8**: 170-179 [PMID: 15153235 DOI: 10.1186/cc2418]
- 42 **Hiltebrand LB**, Krejci V, Banic A, Erni D, Wheatley AM, Sigurdsson GH. Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. *Crit Care Med* 2000; **28**: 3233-3241 [PMID: 11008987 DOI: 10.1097/00003246-200009000-00019]
- 43 **Albuszies G**, Radermacher P, Vogt J, Wachter U, Weber S, Schoaff M, Georgieff M, Barth E. Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic murine septic shock. *Crit Care Med* 2005; **33**: 2332-2338 [PMID: 16215389 DOI: 10.1097/01.CCM.0000182817.20977.E9]
- 44 **La Mura V**, Pasarín M, Rodriguez-Vilarrupla A, García-Pagán JC, Bosch J, Abralde JG. Liver sinusoidal endothelial dysfunction after LPS administration: a role for inducible-nitric oxide synthase. *J Hepatol* 2014; **61**: 1321-1327 [PMID: 25038487 DOI: 10.1016/j.jhep.2014.07.014]
- 45 **Spapen H**. Liver perfusion in sepsis, septic shock, and multiorgan failure. *Anat Rec (Hoboken)* 2008; **291**: 714-720 [PMID: 18484618 DOI: 10.1002/ar.20646]
- 46 **Richards ER**, Kabir SI, McNaught CE, MacFie J. Effect of thoracic epidural anaesthesia on splanchnic blood flow. *Br J Surg* 2013; **100**: 316-321 [PMID: 23203897 DOI: 10.1002/bjs.8993]
- 47 **Eipel C**, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. *World J Gastroenterol* 2010; **16**: 6046-6057 [PMID: 21182219 DOI: 10.3748/wjg.v16.i48.6046]

P- Reviewer: Yang ZJ S- Editor: Ji FF L- Editor: A
E- Editor: Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Critical Care Medicine*

World J Crit Care Med 2015 May 4; 4(2): 105-151



Editorial Board

2011-2015

The *World Journal of Critical Care Medicine* Editorial Board consists of 246 members, representing a team of worldwide experts in critical care medicine. They are from 45 countries, including Argentina (2), Australia (8), Austria (2), Bangladesh (1), Belgium (3), Brazil (4), Canada (7), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (8), Germany (11), Greece (9), Hungary (1), India (10), Iran (2), Ireland (1), Israel (6), Italy (14), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (3), Singapore (1), Slovenia (1), South Africa (1), Spain (7), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (8), United States (72), and Uruguay (1).

EDITOR-IN-CHIEF

Yaseen Mohamed Arabi, *Riyadh*

GUEST EDITORIAL BOARD MEMBERS

Hsing I Chen, *Hualien*
Sheng-Hsien Chen, *Tainan*
Yih-Sharnng Chen, *Taipei*
Yung-Chang Chen, *Taipei*
Der-Yang Cho, *Taichung*
Cheng-Keng Chuang, *Taoyuan*
How-Ran Guo, *Tainan*
Bang-Gee Hsu, *Hualien*
Chien-Wei Hsu, *Kaohsiung*
Wen-Jinn Liaw, *Taipei*
Yan-Ren Lin, *Changhua*
Jiunn-Jye Sheu, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Eduardo Chuluyan, *Buenos Aires*
Adrian Angel Inchauspe, *Berazategui*



Australia

Zsolt J Balogh, *Newcastle*
Zoltan Huba Endre, *Sydney*
Nam Q Nguyen, *Adelaide*
Alistair D Nichol, *Melbourne*
Srinivas Rajagopala, *Adelaide*
Georg Marcus Schmolzer, *Melbourne*
Andrew Trevitt Slack, *Southport*
Ravindranath Tiruvoipati, *Frankston*



Austria

Lars-Peter Kamolz, *Vienna*
Sylvia Knapp, *Vienna*



Bangladesh

Saidur Rahman Mashreky, *Dhaka*



Belgium

Teresinha Leal, *Brussels*
Manu Malbrain, *Antwerp*
Jean-Louis Vincent, *Brussels*



Brazil

Luciano CP Azevedo, *São Paulo*
Patricia Rieken Macedo Rocco, *Rio de Janeiro*
Marcos Antonio Rossi, *São Paulo*
Renato Seligman, *Porto Alegre*



Canada

Douglas D Fraser, *London*
Pierre A Guertin, *Quebec*
Marc Jeschke, *Toronto*
Constantine J Karvellas, *Edmonton*
Wolfgang Michael Kuebler, *Toronto*
Mingyao Liu, *Toronto*
Xi Yang, *Manitoba*



China

Xiang-Dong Chen, *Chengdu*

Xu-Lin Chen, *Hefei*
Wong Tak Chuen, *Hong Kong*
Ming-Xu Da, *Gansu*
Huang-Xian Ju, *Nanjing*
Ting-Bo Liang, *Hangzhou*
Peng-Lin Ma, *Beijing*
Chung-Wah David Siu, *Hong Kong*
Yong-Ming Yao, *Beijing*
Jia-Ping Zhang, *Chongqing*
Wei-Dong Zhou, *Beijing*



Croatia

Alan Sustic, *Rijeka*



Cuba

Jesús Pérez-Nellar, *La Habana*



Denmark

Dan Stieper Karbing, *Aalborg*



Egypt

Ibrahim Abouomira, *Cairo*
Hanan Ibrahim, *Cairo*
Amr M Moghazy, *Alexandria*
Ayman A Yousef, *Tanta*



Finland

Asko Armas Riutta, *Tampere*

**France**

Jean-Marc Cavaillon, *Paris*
 Jean-Michel Constantin, *Clermont-Ferrand*
 Marc Leone, *Marseille*
 Bruno Mégarbane, *Paris*
 Saad Nseir, *Lille*
 Nicolas Terzi, *Caen*
 Jean-François Timsit, *La Tronche Cedex*
 Benoit Vallet, *Lille*

**Germany**

Hendrik Bracht, *Ulm*
 Michael Czaplik, *Aachen*
 Gerrit Grieb, *Aachen*
 Tobias Keck, *Freiburg*
 Philipp Kobbe, *Aachen*
 Alexander Koch, *Aachen*
 Marc Maegele, *Cologne*
 Norbert Pallua, *Aachen*
 Andrzej Antoni Piatkowski, *Aachen*
 Armin Rudolf Sablotzki, *Leipzig*
 Kai D Zacharowski, *Frankfurt am Main*

**Greece**

Ioanna Dimopoulou, *Athens*
 Dimitrios Karakitsos, *Athens*
 Petros Kopterides, *Athens*
 Gregory Kouraklis, *Athens*
 Athanasios D Marinis, *Athens*
 George Nakos, *Ioannina*
 Papaioannou E Vasilios, *Alexandroupolis*
 Theodoros Xanthos, *Athens*
 Spyros G Zakyntinos, *Athens*

**Hungary**

Zoltan Rakonczay, *Szeged*

**India**

Rachna Agarwal, *Delhi*
 Ritesh Agarwal, *Chandigarh*
 Mohammad Farooq Butt, *Srinagar*
 Mohan Gurjar, *Lucknow*
 Deven Juneja, *New Delhi*
 Farhad N Kapadia, *Mumbai*
 Vikram Kate, *Pondicherry*
 Pramod Kumar, *Manipal*
 Ritesh G Menezes, *Mangalore*
 Medha Mohta, *Delhi*

**Iran**

Hemmat Maghsoudi, *Tabriz*
 Homayoun Sadeghi-Bazargani, *Tabriz*

**Ireland**

Sanjay H Chotirmall, *Dublin*

**Israel**

Alexander Becker, *Kefar Tavor*
 Yoram Kluger, *Haifa*
 Yona Kosashvili, *Zerrifin*
 Kobi Peleg, *Tel Aviv*
 Ilan Sela, *Rehovot*
 Pierre Singer, *Tel Aviv*

**Italy**

Giacomo Bellani, *Monza*
 Giovanni Camussi, *Torino*
 Anselmo Caricato, *Rome*
 Piero Ceriana, *Pavia*
 Antonio Chiaretti, *Rome*
 Davide Chiumello, *Milano*
 Alfredo Conti, *Messina*
 Paolo Cotogni, *Torino*
 Daniele M De Luca, *Rome*
 Vincenzo De Santis, *Rome*
 Luca La Colla, *Parma*
 Giovanni Landoni, *Milano*
 Raffaele Scala, *Lucca*
 Giovanni Vento, *Rome*

**Japan**

Keishiro Aoyagi, *Kurume*
 Satoshi Hagiwara, *Yufu*
 Yuichi Hattori, *Toyama*
 Hideo Inaba, *Kanazawa*
 Eisuke Kagawa, *Hiroshima*
 Chieko Mitaka, *Tokyo*

**Jordan**

Feras Ibrahim Hawari, *Amman*

**Mexico**

Silvio A Ñamendys-Silva, *Mexico City*

**Morocco**

Redouane Abouqal, *Rabat*

**Netherlands**

WA Buurman, *Maastricht*
 Martin CJ Kneyber, *Groningen*
 Patrick Schober, *Amsterdam*
 Arie Barend Van Vugt, *Enschede*

**New Zealand**

Sultan Zayed Al-Shaqsi, *Dunedin*
 Arman Adam Kahokehr, *Whangarei*
 John William Pickering, *Christchurch*

**Norway**

Ulf R Dahle, *Oslo*

**Poland**

Maciej Owecki, *Poznań*

**Portugal**

Ernestina Rodrigues Gomes, *Porto*
 Cristina Granja, *Porto*
 José António Lopes, *Lisbon*
 Pedro M Póvoa, *Lisbon*

**Russia**

Konstantin A Popugaev, *Moscow*

**Saudi Arabia**

Imran Khalid, *Jeddah*
 Mohamed Taifour Suliman, *Tabuk*

**Singapore**

Devanand Anantham, *Singapore*

**Slovenia**

Štefek Grmec, *Maribor*

**South Africa**

DL Clarke, *Pietermaritzburg*

**Spain**

Juan Carlos Montejo González, *Madrid*
 David Jimenez, *Madrid*
 Juan Antonio Llompарт-Pou, *Palma*
 Antonio Torres Mart, *Barcelona*
 Enrique Ariel Piacentini, *Barcelona*
 Alonso Mateos Rodriguez, *Madrid*
 R Rodríguez-Roisin, *Barcelona*

**Sweden**

Mihai Oltean, *Gothenburg*

**Switzerland**

Dieter Cadosch, *Zurich*
 Mihael Potocki, *Basel*
 John Friedrich Stover, *Zurich*

**Thailand**

Viroj Wiwanitkit, *Bangkok*

**Tunisia**

Mabrouk Bahloul, *Sfax*

**Turkey**

Yusuf Kenan Coban, *Malatya*
Bensu Karahalil, *Ankara*
Ali Nayci, *Mersin*

**United Kingdom**

Sammy Al-Benna, *Nottingham*
Giles N Cattermole, *London*
Frantisek Duska, *Nottingham*
James Nicholas Fullerton, *London*
Christina Jones, *Prescot*
Sameer Khan, *Middlesbrough*
George Ntoumenopoulos, *London*
Cecilia O'Kane, *Belfast*

**United States**

Edward Abraham, *Winston-Salem*
Bernard R Bendok, *Chicago*
Michael Blaivas, *Atlanta*

Charles D Boucek, *Pittsburgh*
Marcia Leigh Brackbill, *Winchester*
Ronald A Bronicki, *Houston*
Robert C Cantu, *Concord*
Marylou Cardenas-Turanzas, *Houston*
Archana Chatterjee, *Omaha*
Paul A Checchia, *St. Louis*
Rubin Issam Cohen, *New Hyde Park*
Stephen Cohn, *San Antonio*
Donald Edward Craven, *Burlington*
Ruy J Cruz Jr, *Pittsburgh*
Francis C Dane, *Roanoke*
Marc de Moya, *Boston*
Steven M Donn, *Ann Arbor*
Christopher P Farrell, *Wynnwood*
Marco Fernández, *Nashville*
Kevin Foster, *Phoenix*
Barry D Fuchs, *Philadelphia*
Richard P Gonzalez, *Mobile*
Kenneth W Gow, *Seattle*
Alan H Hall, *Laramie*
Jijo John, *Oklahoma City*
Lewis J Kaplan, *New Haven*
Jason N Katz, *Chapel Hill*
Salah Georges Keyrouz, *Little Rock*
Deborah A Kuhls, *Las Vegas*
Gregory Luke Larkin, *New Haven*
Christos Lazaridis, *Charleston*
James Anthony Lin, *Los Angeles*
Yahia M Lodi, *Syracuse*
Roger M Loria, *Richmond*
Aigang Lu, *Cincinnati*
Rudolf Lucas, *Augusta*
O John Ma, *Portland*
Robert T Mallet, *Fort Worth*
William T McGee, *Springfield*
Mark G McKenney, *Miami*

Michael Moussouttas, *Philadelphia*
Oliver Hans-Josef Muensterer, *Birmingham*
Rahul Nanchal, *Milwaukee*
Michael Steven Niederman, *Mineola*
Gary Frank Nieman, *Syracuse*
James Martin O'Brien, *Columbus*
Martin Oudega, *Pittsburgh*
Catherine Mobley Preissig, *Duluth*
Virginia Prendergast, *Phoenix*
Ramesh Raghupathi, *Philadelphia*
Miren Ava Schinco, *Jacksonville*
Carl Ivan Schulman, *Miami*
L Keith Scott, *Shreveport*
Kevin Navin Sheth, *Baltimore*
Jenni Short, *Salina*
Ronald Fong Sing, *Charlotte*
Philip Charles Spinella, *St. Louis*
Robert M Starke, *Charlottesville*
Stanislaw Peter A Stawicki, *Columbus*
David Christopher Stockwell, *Washington*
Stanislav Svetlov, *Gainesville*
Maged A Tanios, *Long Beach*
Neal James Thomas, *Hershey*
Nancy Moon Tofil, *Birmingham*
Balagangadhar R Totapally, *Miami*
Steven Nicholas Vaslef, *Durham*
Joseph Clark Watson, *Falls Church*
John Stephen Wilgis, *Orlando*
David Conrad Willms, *San Diego*
Haodong Xu, *Rochester*
Xiao-Ming Xu, *Indianapolis*
Midori Anne Yenari, *San Francisco*

**Uruguay**

William Manzanares, *Montevideo*



REVIEW

- 105 Anticoagulant modulation of inflammation in severe sepsis
Allen KS, Sawheny E, Kinasewitz GT
- 116 Fluid and electrolyte overload in critically ill patients: An overview
Besen BAMP, Gobatto ALN, Melro LMG, Maciel AT, Park M

MINIREVIEWS

- 130 Tumor lysis syndrome: A clinical review
Mirrahimov AE, Voore P, Khan M, Ali AM
- 139 Designing drug regimens for special intensive care unit populations
Erstad BL

Contents

World Journal of Critical Care Medicine
Volume 4 Number 2 May 4, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Saad Nseir, MD, ICU, Calmette Hospital, bd du Pr Leclercq, 59037 Lille Cedex, France

AIM AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, and application of bronchofiberscopy in critically ill patients.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Critical Care Medicine is now indexed in PubMed Central, PubMed, Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Mei Gong*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Yaseen Mohamed Arabi, MD, FCCP, FCCM, Associate Professor, Chairman, Intensive Care Department, King Saud Bin Abdulaziz University, Medical Director, Respiratory Services, King Abdulaziz Medical City, National Guard Hospital, Riyadh, PO Box 22490, Riyadh 11426, Saudi Arabia

Derek S Wheeler, MD, FAAP, FCCP, FCCM, Associate Professor, Associate Patient Safety Officer, Medical Director, Pediatric Intensive Care Unit, Division of Critical Care Medicine, James M. Anderson Center for Health Systems Excellence, The Center for Simulation and Research, Co-Director, The Center

for Acute Care Nephrology, Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>

<http://www.wjnet.com>

PUBLICATION DATE

May 4, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Anticoagulant modulation of inflammation in severe sepsis

Karen S Allen, Eva Sawheny, Gary T Kinasewitz

Karen S Allen, Eva Sawheny, Gary T Kinasewitz, Section of Pulmonary and Critical Care, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest: All authors have no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Karen S Allen, MD, Assistant Professor of Medicine, Section of Pulmonary and Critical Care, University of Oklahoma Health Sciences Center, 920 Stanton L Young Blvd WP1310, Oklahoma City, OK 73104, United States. karen-allen@ouhsc.edu

Telephone: +1-405-2716173

Received: October 16, 2014

Peer-review started: October 16, 2014

First decision: December 17, 2014

Revised: January 13, 2015

Accepted: February 4, 2015

Article in press: February 9, 2015

Published online: May 4, 2015

ill with a high expected mortality may be shown to benefit from such therapy, at the present time none of these anticoagulants are neither approved nor can they be recommended for the treatment of sepsis.

Key words: Inflammation; Protein C; Heparin; Tissue factor pathway inhibitor; Thrombomodulin; Antithrombin; Sepsis; Coagulation; Neutrophil extracellular traps

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The interaction between the coagulation and inflammatory cascade contributes to the overall pathophysiology of severe sepsis. These processes become unchecked and thus can lead to significant morbidity and mortality. Many anticoagulants have been studied in clinical trials as a means to modulate the inflammatory and coagulation cascade with the aim to improve outcomes for septic patients *via* modulation of these cascades. This article outlines the pathophysiology and interaction between inflammation and coagulation in severe sepsis and also reviews the anticoagulants previously studied for modulation.

Abstract

Inflammation and coagulation are so tightly linked that the cytokine storm which accompanies the development of sepsis initiates thrombin activation and the development of an intravascular coagulopathy. This review examines the interaction between the inflammatory and coagulation cascades, as well as the role of endogenous anticoagulants in regulating this interaction and dampening the activity of both pathways. Clinical trials attempting to improve outcomes in patients with severe sepsis by inhibiting thrombin generation with heparin and/or endogenous anticoagulants are reviewed. In general, these trials have failed to demonstrate that anticoagulant therapy is associated with improvement in mortality or morbidity. While it is possible that selective patients who are severely

Allen KS, Sawheny E, Kinasewitz GT. Anticoagulant modulation of inflammation in severe sepsis. *World J Crit Care Med* 2015; 4(2): 105-115 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i2/105.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i2.105>

INTRODUCTION

Sepsis is a leading cause of mortality in the United States responsible for more than 200000 deaths each year. The overall mortality is estimated to be approximately 28.6% for all age groups with mortality increasing in the elderly^[1]. Furthermore, the incidence of sepsis is increasing secondary to increased use of immunosuppression therapy, invasive procedures,

transplantation, and chemotherapy. Mortality in sepsis is frequently due to organ failure and the risk of mortality increases with the number of failing organs. Individuals with sepsis and three or more failing organs have a 70% mortality rate compared to a mortality rate of 15% without organ failure^[2].

Much of the organ failure in sepsis is thought to be caused by microvascular thrombosis. Local thrombus formation is protective when an infection is localized as it works to prevent bacteria spread systemically to other organs. However, once the infection spreads to the blood stream and sepsis develops, the formation of thrombi within the microvasculature acts counterproductively and increases organ damage which may lead to organ failure. Significant coagulation disturbances are thought to complicate approximately 35% of all severe sepsis cases^[3]. Small and medium size vessels show fibrin deposition that has been found during autopsy studies of patients with DIC and sepsis. Fibrin is also found in many organs under pathological examination following sepsis^[4]. Measures of coagulation activation in patients with sepsis show that some amount of clotting is present in all patients with septic shock regardless of the presence of overt disseminated intravascular coagulation (DIC)^[4-6].

Inflammation and coagulation are frequently partners in crime in severe sepsis. Studies in the 1990s showed the complex relationship between these two systems in patients with sepsis or a traumatic insult. The inflammatory mediators were shown to activate coagulation and vice versa as inflammation may be induced by activation of the coagulation cascade^[7]. The two are linked through similar activation mechanisms *via* a variety of pathways. Ultimately it is thought the uncontrolled systemic expression of both systems which plays a key role in the pathogenesis of multi-organ failure in sepsis. In this review article we will outline the role of inflammatory markers and coagulation in sepsis as well as the intricate relationship between the two. Subsequently, we will then review the results of clinical trials attempting to modulate this inflammation in patients with severe sepsis.

INFLAMMATION AND COAGULATION CASCADE RESPONSE TO SEVERE SEPSIS

The innate immune system responds to bacterial infections initiated by cells which detect pathogen associated molecular patterns (PAMPs) that are expressed on invading bacteria. The damaged tissue and cells from the host in sepsis will release intracellular proteins commonly known as alarmins^[8]. Together alarmins and PAMPs are termed damage-associated molecular patterns (DAMPs). The initial immune response to a pathogen or DAMPs is driven by pattern recognition receptors (PRRs) that are expressed on immune cells. PRR, however, can also be found on other cells which are primary involved in

hemostasis as these are highly conserved receptors. In humans PRRs are mainly reported on platelets as toll-like receptors^[9]. This serves as a key link between the immune and coagulation systems as these cells are also then able to recognize and initiate the inflammatory response. Both toll-like receptors and complement receptors are PRRs which can initiate a complex cellular inflammatory response to pathogen invasion. These PRRs further activate the coagulation system through increased production of tissue factor and impairment of anticoagulation and fibrinolysis^[10].

Activation of the coagulation cascade and thrombus in sepsis are generally thought of as adverse events occurring as a result of pathogen invasion. However, the recently described process of immunothrombosis suggests that some local thrombosis in response to microorganisms may actually be an independent line of host defense against pathogens^[11]. This theory suggests that small amount of clot formation actually is beneficial for the host as bacteria and DAMPs are trapped and kept away from the host circulation, preventing systemic spread of infection and inflammatory cytokines or DAMPs to other organs. The immune system and coagulation systems work closely together *via* cross signaling to produce immunothrombosis. The innate immune cells, particularly monocytes and neutrophils, are recruited to sites of intravascular thrombosis in response to DAMPs at the site. In turn these cells express activated intravascular tissue factor (TF) which enhances clot formation *via* the extrinsic pathway of coagulation^[11].

Although immunothrombosis may have a beneficial effect for the host in localized infection, this is not true in profound system wide infections. Severe sepsis, septic shock, and DIC occur together when the control mechanisms of inflammation and coagulation and the intricate relationship between these two breaks down and each proceeds unchecked. The crosstalk between each system may actually perpetuate this process in severe systemic infection. There are several key aspects of the coagulation cascade which, when up-regulated, have a significant impact and are then in turn influenced by the immune system; these include TF, thrombin, and platelets. Likewise, cells which are part of the inflammatory response, particularly neutrophils, and the complement system link inflammation to coagulation during sepsis. Furthermore, the regulation of the coagulation system fails during DIC, endogenous anticoagulant proteins including; tissue factor pathway inhibitor (TFPI), anti-thrombin (AT), and activated protein C (APC) fail to regulate coagulation^[9,11].

TF is thought to have a key role in the connection of sepsis and coagulation. It is up-regulated in sepsis through both activation by inflammatory cytokines and failure of control mechanisms like TFPI^[10]. The cytokine triggers that cause TF to be expressed include; tumor necrosis factor (TNF), interleukin-1 (IL-1), and other inflammatory mediators including complement^[12]. TF is part of the extrinsic pathway of coagulation and in the healthy state, is not exposed on peripheral blood or

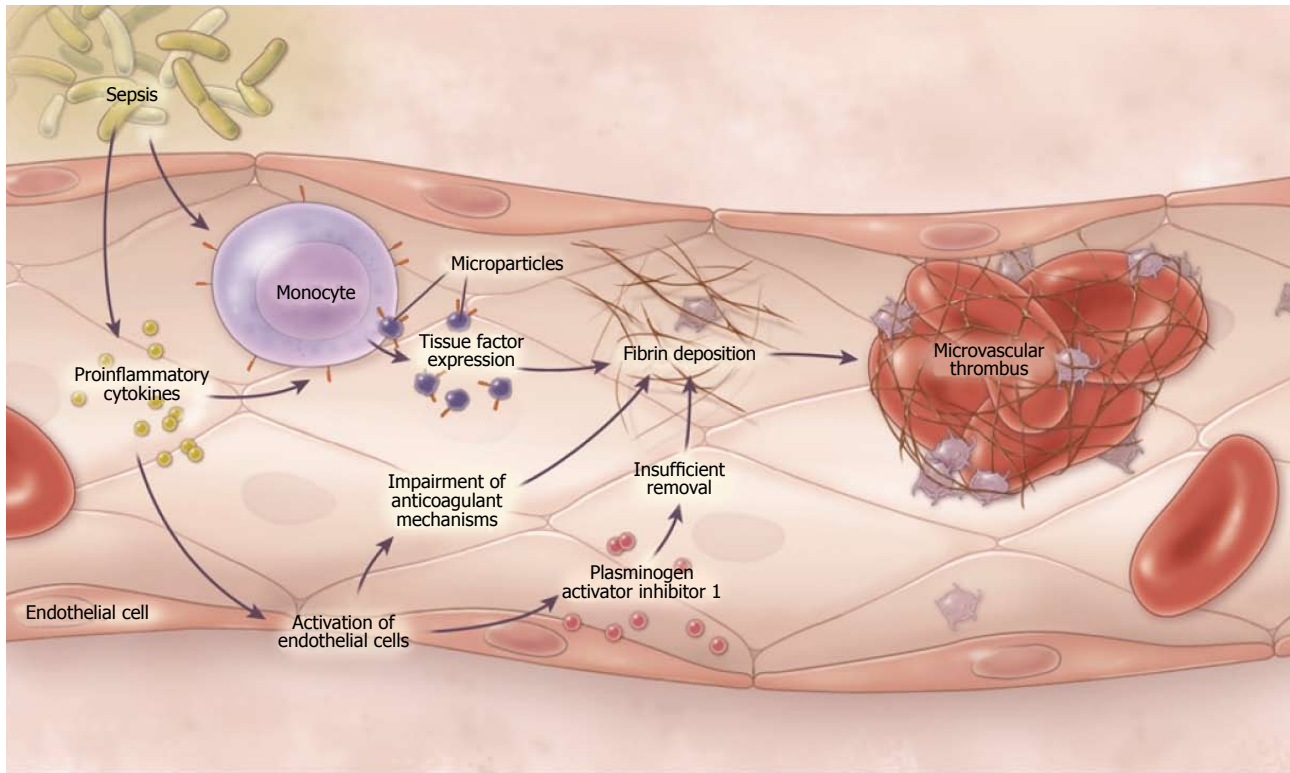


Figure 1 Pathogenesis of disseminated intravascular coagulation in sepsis^[10]. Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anti-coagulant mechanisms and down regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor. Copyright © 2014 Massachusetts Medical Society (used with permission).

endothelial cells although it has a significant presence on extravascular cells^[13]. The physiologic activation of the extrinsic pathway occurs through disruption of the endothelium and exposure of blood to extravascular cells which express TF or in the intravascular space through triggers that cause circulating monocytes, leukocytes, and neutrophils to expose TF on their cell membranes. The latter is thought to be the more common pathway for enhanced expression of TF during pathogen invasion, as the recognition of PAMPs and/or DAMPs by cells of the innate immune system directly enhances TF expression^[11] (Figure 1).

The initiation of coagulation by TF does not always lead to overt DIC in sepsis. Much of the impact of TF on the host response to sepsis may also be due to increasing the inflammatory response. The main inhibitor of TF is TFPI which tightly regulates the interaction of TF with other factors of the extrinsic pathway. TFPI has been studied as a method to modulate the host response to sepsis and through these studies it has become clear that TF has a strong inflammatory contribution during sepsis. Studies have shown that various levels of coagulation are noted in response to sepsis and the effectiveness of TFPI on host survival can be unrelated to differences in coagulation which suggests that much of the beneficial effects of TFPI are from an anti-inflammatory property it can exert on inhibiting TF augmentation of inflammation^[14].

Thrombin, like TF, has a large role in coagulation but also exerts some influence on inflammation during sepsis. Thrombin is the central serine protease mediator of hemostasis. It is activated by Factor Xa and, once active, creates an active feedback loop for continued activation of Factor X. Thrombin also converts soluble fibrinogen to insoluble strands of fibrin for clot formation^[11,15]. Activated thrombin can promote activation of several pro-inflammatory cytokines including, TNF- α , IL- β , and IL-6 as well as generate C5a (part of the complement response to infection) independent of C3. This activity of thrombin is crucial and demonstrates the complex relationships that exist as it shows the crosstalk that occurs between the coagulation system and components of both the inflammatory and complement systems^[15].

Thrombin further actively participates in the inflammatory cascade that occurs during sepsis through specific receptors on platelets, endothelial cells, and white blood cells. These receptors are called protease activated receptors (PARs) and they are responsible for inducing TF emergence from cells and release of plasmin activator inhibitor I or *via* PARs, which inhibits fibrinolysis as well as decreasing thrombomodulin (TM) (a thrombin co-factor that decreases clot formation)^[16]. Thrombin promotes platelet aggregation and activation. The activated platelets express P-selectin after being exposed to thrombin. P-selectin is critical for attachment of white blood cells to endothelial cells and thus initiating

white blood cell activation which contributes to diffuse microvascular injury^[17].

Thrombin is regulated by AT, which is a serum protein with significant enzymatic activity to prevent coagulation and with its broad spectrum of activity it is considered a central inhibitor of the coagulation system. AT forms a complex with thrombin and inactivates it in addition to inhibiting other factors within the coagulation cascade (including the generation of Factors XIIa, XIa, IXa, and Xa). It acts on both the intrinsic and common coagulation pathways *via* inhibiting the action of Factors IXa and Xa respectively^[7]. AT may also have direct anti-inflammatory actions during sepsis beyond its anti-coagulation properties. AT has the ability to inhibit the function of lipopolysaccharide (LPS) signaling on macrophages. This acts to decrease the level of inflammation through blocking macrophage activation. AT may also compete with bacterial pathogens for binding sites on endothelial surfaces and thus prevent endothelial damage by pathogens^[18].

In septic patients with organ failure AT activity is reduced and the degree of reduction is proportional to the severity of sepsis, DIC and organ failure^[16]. Part of this fall in AT levels is likely related to the decreased half-life of AT during sepsis. Typically the half-life of AT is between 36–48 h but decreases to less than 18 h during sepsis^[7]. Additionally, part of the decrease in half-life for AT is related to neutrophil actions. Activated neutrophils release elastase which destroys AT, and therefore significantly decreases natural regulation of the coagulation system.

APC is another endogenous anticoagulant that has additional anti-inflammatory properties as well. Overall the function of protein C is reduced in sepsis and DIC which results in significant compromise of in regulation of coagulation. APC is down-regulated during the host response to sepsis through cytokines and TM loss on the endothelium as well as a decrease in its primary co-factor protein S^[3]. This down-regulation may reflect a conserved part of immunothrombosis and theoretically may be protective in localized tissue infection. However, in sepsis the down-regulation of APC prevents it from actively controlling the host inflammatory response.

APC actually has been found to have an antiinflammatory role during sepsis that may serve partly to keep host response to pathogen invasion in check. APC can decrease apoptosis of endothelial cells and lymphocytes during infection thus reducing DAMPs in the bloodstream which serve to perpetuate further inflammatory reactions. APC also decreases the inflammatory response of key cells; including monocytes, leukocytes and neutrophils. APC decreases NF- κ B signaling which decreases monocyte response to inflammation. APC further acts closely with endothelial cells in an anti-inflammation manner. APC specifically decreases TF up-regulation *via* leukocytes and decreases neutrophils adherence to endothelial cells in response to pathogen invasion^[19].

Thrombin is further regulated by TM which is physiologically found in the intravascular space on vessel

endothelial walls. TM plays a key role in preventing intravascular clot formation under normal physiological conditions. Thrombin binds with TM in a high affinity complex that prevents thrombin from activating fibrinogen to fibrin. The TM-thrombin complex also works as an anti-coagulant and activates protein C which then inactivates Factors Va and VIIIa^[18]. The Thrombin-TM activation of protein C further also acts to decrease the overall inflammatory response to infection by suppressing monocyte-dependent cytokine production^[19].

The Thrombin-TM complex has further influence on the anticoagulation and inflammatory systems. Thrombin activatable fibrinolysis inhibitor (TAFI) activity is increased three-fold by the Thrombin-TM complex formation. TAFI enhances fibrin clot stabilization leading to better control of inflammation as part of immunothrombosis. The activity of TAFI also has systemic anti-inflammatory properties. TAFI inactivates endogenous pro-inflammatory mediators, including bradykinin, osteopontin, and some elements of the complement system (C3 and C5)^[19].

Platelets, like AT and APC, are also frequently decreased in any host response to insult including pathogen invasion. The decrease in platelets is not fully explainable by overt DIC, but rather more likely related to platelet consumption from immunothrombosis and the role platelets play in the inflammatory response. Thrombocytopenia is in fact, a predictor of poor outcome in sepsis and septic shock. This includes severity of thrombocytopenia as well as overall duration of low platelet count indicates poor outcomes^[20].

Platelets have a key role in coagulation and clot formation. Platelets also recognize pathogens *via* PRRs and therefore, stimulate the host inflammatory response. An important example of cross-linkage between inflammation and coagulation *via* PRRs is toll-like receptor 4 (TLR4) (a subfamily of PRRs) on platelet cells, which recognize DAMPs and play an intricate role in activating neutrophils in the immune response^[15]. TLR4 on platelets recognizes PAMPs of pathogens specifically LPS of gram negative bacteria. These receptors also recognize endogenous DAMPs which include heat shock proteins and fibronectin^[21]. Platelets are further able to present microorganisms to neutrophils other immune cells, activating a portion of the innate immune system.

In addition to pathogen recognition, platelets up-regulate and alter the host immune response to pathogens. Platelets, for example, assist in recruiting and enhancing the microbicidal activity of leukocytes by releasing multiple mediators in the bloodstream. Platelets also act to recruit innate immune cells at the site of infection. In addition to recognizing DAMPs, platelets also release DMAPs which promotes additional TF and likely increases thrombosis intravascularly. This process was likely conserved in host immune response as part of the concept of immunothrombosis. Finally, platelets directly bind to neutrophils during the host

response to bacterial infection which subsequently stimulates the formation of neutrophil extracellular traps, although the exact methodology behind this is not known^[11,22].

Neutrophils are terminally differentiated cells that are involved in the early immune response to invading microbes. Neutrophils are directed by cytokines to infected tissue where the cell is activated and may engulf a pathogen for intracellular killing. Neutrophils may also act through extracellular traps or NETs. NETs are composed of chromatin complexes with granular proteins which bind both Gram negative and positive bacteria and effectively kill microbes in an extracellular matrix. The NET releases cellular components that have antibacterial properties including DNA, myeloperoxidase and elastase and histones. The release of these components into the circulation can have unintended harmful effects on the host during sepsis through activation of the coagulation cascade^[8].

NETs can activate coagulation *via* multiple mechanisms. NETs deliver TF to the extracellular surface and thus activate the extrinsic coagulation pathway. The NET surface is polyanionic and can activate certain contact phase proteins like Factor XII. They further stimulate platelet activation *via* histones H3 and H4 specifically. These histones also promote the extrinsic pathway through damage to the endothelial wall. Finally, NETs inactivate TFPI and TM through a complex enzyme pathway. The inactivity of these endogenous anticoagulants further leads to uncontrolled coagulation during DIC. Much of the coagulation function of NETs is proposed to be protective of the host as immunothrombosis to contain pathogens at an infectious site. However, in systemic infection the protective process becomes destructive through unchecked inflammation and coagulation^[11].

The complicated and complex interactions between the traditional coagulation system and the inflammatory system are further complicated by the role of complement during sepsis and DIC. Complement can be viewed as an "alarm system" which can recognize DAMPs and respond to both infectious and non-infectious changes within the host^[23]. The complement system is crucial to host defense against invading microbes. It is well known that deficiency in some components of complement can make an individual susceptible to increased risk of infection. For example, deficiency in opsonization contributes to increased susceptibility to infections by pyogenic bacteria including *Haemophilus influenza* and *S. pneumoniae*. However during multi-organ failure secondary to sepsis, complement is thought to have a detrimental effect on the host and contribute to organ failure^[24].

Complement and in particular C5a can have harmful effects during sepsis that act through both inflammation and coagulation dis-regulation. High levels of C5a act to decrease the effectiveness of neutrophils by blocking the NADPH formation of superoxide anions essential

for killing gram negative bacteria. Then in turn C5a can increase the function of macrophages causing increased or overproduction of cytokines which contribute to the cytokine storm of sepsis. C5a further enhances the expression of TF therefore disrupting the coagulation balance further. Finally C5a increases the apoptosis of thymocytes decreasing B cell production and leading to an immunodeficiency state in late sepsis^[25]. Sepsis and the resulting multi-organ failure are clearly much more complex of a process to be explained by unregulated inflammation or coagulation alone. Instead, it is an intricate web with multiple cross-talk interactions between the various components of each system. This intricate web is the over-riding etiology that leads to sustained multi-organ failure which causes host demise. These are numerous targets within these systems that may be targeted as therapy to augment the overall host response to overwhelming sepsis. Many of the initial clinical trials in sepsis focused on blocking various components of the inflammatory cascade in sepsis. When these trials failed to show a significant improvement in morbidity or mortality it was natural to turn to modifying the coagulant response in an attempt to influence the outcome. Key clinical trials which investigate anticoagulants in an attempt to improve outcomes in septic patients will be reviewed in the following sections.

ANTICOAGULANT EFFECTS ON SEVERE SEPSIS

Antithrombin

AT is an endogenous anticoagulant synthesized by the liver. As its name implies, AT inhibits thrombin as well as factors Xa, IXa, VIIa, XIa, and XIIa. In addition to its anticoagulant effect, AT also has an anti-inflammatory effect at high serum levels. AT binds to glycosaminoglycans on the endothelial cell surface and enhances the microvascular production of prostacyclin I₂, a potent vasodilator and inhibitor of platelet function^[26].

AT levels are decreased in patients with severe sepsis, and this is associated with a worse prognosis. Several small studies initially suggested that AT administration could have a beneficial effect on organ function and survival in patients with severe sepsis. AT was subsequently studied in the phase 3 KyberSept trial. This study was a large ($n = 2314$) double blind, placebo controlled, multicenter trial, to determine if high dose AT would provide a survival advantage in patients with severe sepsis^[27]. There was no significant effect on the overall mortality at 28 d, 38.9% in the AT group vs 38.7% in the placebo group. However, these results may have been complicated as the concurrent use of low dose heparin for venous thromboembolism prophylaxis was allowed in this study (Table 1).

The simultaneous use of heparin competitively inhibits the binding of AT to other glycosaminoglycans and may have affected the efficacy of AT. Also, AT must

bind to glycosaminoglycans on endothelial surfaces to promote local anticoagulant and anti-inflammatory activity^[16]. In the subgroup of patients who did not receive concomitant heparin during the treatment phase, the 28 d mortality was lower in the AT group (37.8%) than in the placebo group (43.6%) but this difference did not reach statistical significance ($P = 0.08$). This mortality trend, however, became significant after 90 d, 44.9% in the AT group vs 52.5% in the placebo group, suggesting that there might be a role for AT therapy in the absence of heparin.

The KyberSept trial examined the results of high dose AT on patient with severe sepsis irrespective of DIC status. Wiedermann *et al.*^[28] in a subsequent analysis evaluated patients in the KyberSept trial with DIC and noted an absolute reduction in 28 d mortality of 14.6% compared to placebo ($P = 0.02$), whereas no effect on 28 d mortality of patients without DIC was seen^[28]. A systematic review by Wiedermann suggested that the administration of AT to septic patients with DIC may increase overall survival. AT is approved and is currently being used for the treatment of DIC (including sepsis related DIC) in Japan.

Several studies from Japan have showed positive outcomes from AT use in severe sepsis. A recent small randomized controlled, multicenter trial by Gando *et al.*^[29], evaluated the efficacy of a supplemental dose of AT for septic patients with DIC. They enrolled septic patients with DIC and AT levels of 50%-80% normal. The patients were randomly assigned to receive supplemental doses of AT or placebo for 3 d. They noted that AT treatment resulted in significantly decreased DIC scores and better recovery rates from DIC compared with a control group without an increased incidence of bleeding complications. Tagami *et al.*^[30] identified 9075 patients with severe pneumonia and sepsis related DIC in a nationwide Japanese database^[30]. Using propensity matching to account for confounding factors, they identified 2194 pairs of matched patients who did or did not receive AT treatment. They noted a beneficial effect of AT on 28 d mortality (confidence interval 40.6% vs 44.2%) and adjusted odds ratio favoring AT use. A prospective multicenter study from Japan compared 1500 IU/d vs 3000 IU/d supplemental dose of AT in septic DIC patients. It noted that the AT dose of 3000 IU/d improved survival. AT has been studied extensively and is widely used for the treatment of sepsis related DIC in Japan, however, it remains unavailable for the treatment of severe sepsis or sepsis related DIC in other countries.

Protein C

Protein C has multiple actions within both the coagulation and inflammation pathways. Low levels of protein C are associated with a poor outcome in patients with severe sepsis, suggesting repletion of protein C may benefit these patients. Protein C is converted by thrombin into APC which is an endogenous anticoagulant that inhibits

activated cofactors V and VIII, thereby reducing thrombin generation. In addition to its ability to reduce thrombin generation, APC also has anti-inflammatory properties that are independent of its effect on thrombin generation.

Numerous basic science research studies have demonstrated potentially advantageous effects of APC. Extracellular histones released in response to an inflammatory challenge contribute to endothelial dysfunction, organ failure and death during sepsis. APC enhances histone degradation of histones^[31], which may account for the cytoprotective activities of APC which include anti-apoptotic activity, anti-inflammatory activity, and endothelial barrier stabilization^[32]. Protein C levels are decreased in patients with sepsis and recovery of protein C levels is associated with improved survival. Thus it would seem logical to examine its efficacy as a therapeutic agent.

The Prospective Recombinant Human APC Worldwide Evaluation in Severe Sepsis (PROWESS) trial evaluated the effects of recombinant APC (rhAPC) in patients with severe sepsis^[33]. This was the first phase 3 clinical trial to demonstrate improved survival in patients with severe sepsis. PROWESS was a randomized, double blind placebo-controlled multicenter trial which was stopped early because of the improved survival observed in the treated group. The overall mortality rate was 30.8% in the placebo group and 24.7% in the APC group, a reduction of 6.1% (relative risk reduction of 19.4%). The survival benefit was greatest in the sickest patients, those with the most organ failures and highest APACHE II scores. Patients with overt DIC had an absolute reduction in mortality from 40.3% to 30.5%, which is a relative risk reduction of 29.1%^[34]. The bleeding event rate was only 3.4%. Subgroup analysis indicated that the mortality benefit was limited to patient with increased illness severity. Based on this study, rhAPC was approved by the Food and Drug Administration in 2001 for the treatment of severe sepsis in patients with an APACHE II of 24 or greater; the median APACHE II score in the PROWESS study.

A subsequent open label trial (ENHANCE) confirmed the mortality rate of approximately 25% in patients with severe sepsis but left open the question of whether rhAPC would be beneficial in less sick patients^[35]. The ADDRESS trial randomized 2640 patients with severe sepsis and a single organ failure or APACHE II < 25 to either rhAPC or placebo^[36]. There was no difference in survival in these less severely ill patients, but the rate of serious bleeding with rhAPC was 2.4%, double that of the control patients. A subsequent trial focusing on the severely ill patient with septic shock (PROWESS - SHOCK) failed to confirm the improved outcomes noted in the original PROWESS trial, and in 2011 rhAPC was withdrawn from the world market^[37].

The mortality rates in the PROWESS-SHOCK trial were substantially lower than expected given the inclusion criteria of septic shock, 26.6% vs 24.2% in the APC and control groups respectively. APC did not reduce

Table 1 Previous trials of anticoagulant therapy in severe sepsis

Ref.	Year	Inclusion criteria	n	Design	Therapy	Primary outcome	Treatment	Control	P value
AT									
Warren <i>et al</i> ^[27] (Kybersept)	2001	Severe sepsis	2314	Phase 3 RCT	AT 30000 IU × 96 h or placebo	Mortality	450/115 (38.9%)	446/1157 (38.7%)	0.94
Gando <i>et al</i> ^[29]	2013	Sepsis	60	Prospective randomized	AT 30 IU/kg × 72 h or placebo	DIC recovery (%) on day 3	16/30 (53.3%)	6/30 (20%)	0.015
Tagami <i>et al</i> ^[30]	2014	Sepsis-associated DIC in severe pneumonia	4388	Retrospective, propensity matched	AT 1500 IU/d	Mortality	890/2194 (40.6%)	270/2194 (44.2%)	0.02
rAPC									
Bernard <i>et al</i> ^[33] (Prowess trial)	2001	Severe sepsis	1690	Phase 3 RCT	APC 24 µg/kg per hour × 96 h or placebo	Mortality	210/850 (24.7%)	259/840 (30.8%)	0.005
Vincent <i>et al</i> ^[35] (Enhance trial)	2005	Severe sepsis	2378	Prospective single arm multicenter	APC 24 µg/kg per hour × 96 h	Mortality	25.30%	NA	NA
Abraham <i>et al</i> ^[36] (Address trial)	2005	Severe sepsis with APACHE < 25	2613	Phase 3 RCT	APC 24 µg/kg per hour × 96 h or placebo	Mortality	243/1316 (18.5%)	220/1297 (17%)	0.34
Ranieri <i>et al</i> ^[37] (Prowess shock)	2012	Septic shock	1680	Phase 3 RCT	APC 24 µg/kg per hour × 96 h or placebo	Mortality	223/846 (26.4%)	202/834 (24.2%)	0.31
Rimmer <i>et al</i> ^[38]	2012	Severe sepsis with septic shock	933	Retrospective, 2:1 propensity matched	APC 24 µg/kg per hour × 96 h	Mortality	180/311 (34.7%)	254/622 (40.8%)	0.05
Thrombomodulin									
Saito <i>et al</i> ^[43]	2007	DIC associated with hematologic malignancy or infection	234	Phase 3 RCT	Thrombomodulin 0.06 mg/kg × 6 d or heparin 8 U/kg per hour × 6 d	DIC recovery (%) on day 7	74/112 (66.1%) (thrombomodulin)	56 (49.9%) (heparin)	0.027
Vincent <i>et al</i> ^[44]	2013	Sepsis with DIC	741	Phase 2 RCT	Thrombomodulin 0.06 mg/kg × 6 d or placebo	Mortality	66/371 (17.8%)	80/370 (21.6%)	0.273
Heparin									
Jaimes <i>et al</i> ^[47] (HETRASE study)	2009	Sepsis	317	RCT	Heparin 500 U/h × 7 d or placebo	LOS	12 d (median)	12.5 d (median)	0.976
rTFPI									
Abraham <i>et al</i> ^[49]	2001	Severe sepsis	210	Phase 2 RCT	rTFPI 0.025 or 0.05 mg/kg per hour × 96 h or placebo	Mortality	43/141 (30%)	26/69 (38%)	0.3
Abraham <i>et al</i> ^[50] (OPTIMIST trial)	2003	Severe sepsis	1754	Phase 3 RCT	rTFPI 0.025 mg/kg per hour × 96 h or placebo	Mortality	301/880 (34.2%)	296/874 (33.9%)	0.88
Wunderink <i>et al</i> ^[52] (CAPTIVATE trial)	2011	Severe sepsis with community acquired pneumonia	2102	Phase 3 RCT	rTFPI 0.025 mg/kg per hour × 96 h or placebo	Severity adjusted 28 d mortality	185/955 (19.4%)	178/914 (19.5%)	0.56

RCT: Randomized controlled trial; LOS: Length of stay; APC: Activated protein C; DIC: Disseminated intravascular coagulation; TFPI: Tissue factor pathway inhibitor; AT: Anti-thrombin; NA: Not available.

mortality at 28 or 90 d, as compared with placebo, but was associated with increased bleeding risks in patients with severe sepsis and septic shock^[37]. A subsequent retrospective multicenter cohort study of patients with septic shock, early use of APC was associated with 6.1% absolute reduction in 30 d mortality^[38]. Another meta-analysis by Kalil *et al*^[39], noted a significant reduction in hospital mortality (18%), and increased bleeding rate (5.4%) with the real life use of APC compared with controls.

Although rhAPC is no longer accessible, plasma derived APC is available in Japan. A randomized double

blind trial compared the efficacy and safety of plasma derived APC with unfractionated heparin in the treatment of DIC by a Japanese group^[40]. No significant difference in the rate of complete recovery from DIC was seen between the 2 groups. The rate of death from any cause within 28 d after treatment was 20.4% in the APC group, significantly lower than the 40% death rate observed in the heparin group ($P < 0.05$). There were no severe adverse events in either group. These findings suggests that plasma derived APC as a remarkably reduced dose compared to rhAPC can improve DIC, without increasing bleeding and its effects should be evaluated in future

trials.

TM

TM is an endogenous anticoagulant located on the surface of the endothelial cell that acts by inhibiting thrombin mediated clot formation and enhancing protein C activation at the site of clotting. In addition to its anticoagulant activity, TM also has anti-inflammatory properties, including interfering with the activation of complement and inactivating high-mobility group protein B1, a mediator associated with mortality in late sepsis^[41]. TM expression on the endothelial surface is down regulated in patients with sepsis and may contribute to the development of DIC. Replacement of TM, therefore, may offer therapeutic value^[42].

Saito *et al.*^[43], evaluated the efficacy of recombinant TM in treating DIC in a randomized, multicenter, double blind controlled trial. Recombinant TM or unfractionated heparin was administered to patients with DIC due to either malignancy or sepsis and resolution of DIC was assessed after 7 d^[43]. DIC resolved in 66.1% of the group that received recombinant TM, as compared with 49.9% of the heparin groups, respectively ($P < 0.05$). The incidence of bleeding related adverse events was lower in the recombinant TM group 43.1% as compared to 56.5% in the heparin group. Based on this study, recombinant TM was approved for the treatment of DIC in Japan in 2008.

Subsequently a phase 2 trial evaluated the safety and efficacy of TM in patient with sepsis and DIC^[44]. In this trial, DIC was diagnosed by a modified scoring system based on the platelet counts and prothrombin time and international normalized ratio (INR). Patients (371) randomized to TM and patients (370) who received placebo were similar at baseline. Twenty eight day mortality was 17.8% in the TM group and 21.6% in the placebo group. There were no significant differences between the two groups in organ dysfunction, inflammatory markers, bleeding thrombotic events or in the development of new infections during the study. In a post hoc analysis, the greatest benefit from TM was seen in patients with at least one organ dysfunction and an INR of greater than 1.4 at baseline. Based on the results of this encouraging study, a phase 3 trial of recombinant TM in patients with sepsis induced DIC and either shock or acute respiratory failure is currently in progress.

Heparin

Heparin is a sulfated polysaccharide with a heterogeneous structure and complex polymerization (MW, 357 kDa). Heparin binds to AT, causing a conformational change that increases the flexibility of the reactive site loop, activating AT. The activated AT then inactivates thrombin and other proteases, including factor Xa. Heparin also binds platelets to inhibit platelet aggregation, resulting in a strong anticoagulant effect. Heparin at high concentrations prevents histone interactions with

platelets, which is a possible therapeutic target to modulate inflammation in severe sepsis. Fuchs *et al.*^[45], noted that heparin is highly sulfated and rich in negative charges, and electrostatic interactions with histones, are responsible for its histone-neutralizing effects, which suggests heparin could prevent cytotoxicity and collateral organ damage from histones.

Interest in heparin as a therapeutic agent in sepsis was spurred by the observation of Doshi *et al.*^[46], that the use of low dose prophylactic heparin in the placebo arms of KyberSept (phase 3 AT trial) and PROWESS (phase 3 rhAPC trial) was associated with a trend for reduced mortality which was not statistically significant. Heparin use was not randomized in either study and a subsequent study designed to show the safety of concomitant heparin and rhAPC use observed neither benefit nor an increase in bleeding risk. A subsequent retrospective study of 695 propensity matched pairs of patients with septic shock who did or did not receive high dose therapeutic heparin therapy suggested potential reduction in morbidity and mortality with heparin. In the prospective randomized double blind HETRASE Study, 319 patients were randomized to intravenous heparin or placebo. Heparin treatment was safe as there was no increased risk of bleeding. However, there was no significant difference in the primary endpoint, length of hospital stay. Moreover, the heparin treated patients failed to demonstrate a more rapid improvement in organ failure score or increase in survival^[47]. Thus, while heparin is readily available, inexpensive, and widely used for DVT prophylaxis in septic patients, its role in the treatment of sepsis remains undetermined.

TFPI

TF is the major initiator of the blood coagulation process during sepsis and TFPI, an endogenous serine protease inhibitor which is synthesized and secreted by endothelial cells, acts to inhibit both the factor VIIa/TF catalytic complex in a Xa dependent fashion as well as factor Xa directly^[46]. TFPI may also play a role in maintaining endothelial cell integrity^[48].

The initial trial results of recombinant TFPI (rTFPI) administration to patients with severe sepsis were encouraging. A multicenter, randomized placebo controlled, single-blind, dose escalation study enrolled 210 patients who received a continuous infusion of either placebo or rTFPI (dose 0.025 or 0.05 mg/kg per hour) for 4 d. Although the trial was not powered to evaluate mortality, this study noted a trend toward reduction in 28 d all-cause mortality as well as improvement in pulmonary organ dysfunction in the rTFPI group as compared with placebo. Logistic regression modeling suggested a more apparent coagulopathy, manifested by a higher baseline (INR), was associated with more pronounced beneficial TFPI effect^[49].

Subsequently Abraham *et al.*^[50], examined this concept in a phase 3 randomized, double blind, placebo

controlled, multicenter trial which enrolled 1754 patients with severe sepsis and high INR (> 1.2) who were randomly assigned to receive either rTFPI (tifacogin) or placebo. In addition, 201 patients with a low INR (< 1.2) were randomized to receive either rTFPI or placebo. Tifacogin was effective in reducing markers of thrombin activation, but had no effect on 28 d mortality (34.2% with tifacogin vs 33.9% with placebo, $P = 0.88$). Tifacogin administration was associated with an increase in risk of bleeding, irrespective of baseline INR^[50,51]. The most common site of infection in this study was community acquired pneumonia. A post hoc analysis suggested patients, who did not receive concomitant heparin, appeared to benefit from treatment with tifacogin. This led to a large phase 3 trial of rTFPI in patients with severe sepsis from community acquired pneumonia^[53]. Again, rTFPI treated patients demonstrated a greater reduction in markers of thrombin activity, but no improvement in mortality was noted.

CONCLUSION

Inflammation and coagulation are tightly linked with each pathway capable of initiating and amplifying the activity of the other. Full blown expression of the coagulation pathway in the septic patient leads to overt DIC, overt but some degree of coagulation activation is apparent in virtually all patients with severe sepsis. Increasing coagulopathy is associated with the development of organ failures and increased mortality^[53]. Simultaneous with the development of the coagulopathy there is a fall in the levels of endogenous anticoagulants including APC, AT, and TFPI as a consequence of both increased consumption and impaired production. Survivors of severe sepsis have more rapid return of this endogenous anticoagulant to normal levels. Because these endogenous anticoagulants appear to have anti-inflammatory activity independent of their ability to inhibit thrombin generation, they were administered to patients with severe sepsis in an attempt to improve outcomes. One trial of rhAPC showed an improvement in the survival of the sickest patients, but this benefit could not be replicated in subsequent studies. Phase 3 studies of AT and TFPI failed to demonstrate a clear benefit while a Phase 3 trial of TM is still in progress. Anticoagulant therapy in a patient with an underlying coagulopathy increases the risk of bleeding, which may obscure any potential benefit. At this time future trials of anticoagulant therapy for sepsis should focus on the most severely ill patients with the highest expected mortality, as this is the group in which benefit is most likely to be demonstrated. Until they can be shown to reduce morbidity and mortality, anticoagulants should not be used for the treatment of severe sepsis.

REFERENCES

- 1 **Angus DC**, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit*

- Care Med* 2001; **29**: 1303-1310 [PMID: 11445675 DOI: 10.1097/00003246-200107000-00002]
- 2 **Dhainaut JF**, Shorr AF, Macias WL, Kollef MJ, Levi M, Reinhart K, Nelson DR. Dynamic evolution of coagulopathy in the first day of severe sepsis: relationship with mortality and organ failure. *Crit Care Med* 2005; **33**: 341-348 [PMID: 15699837 DOI: 10.1097/01.CCM.0000153520.31562.48]
- 3 **Levi M**. Disseminated intravascular coagulation. *Crit Care Med* 2007; **35**: 2191-2195 [PMID: 17855836 DOI: 10.1097/01.CCM.0000281468.94108.4B]
- 4 **Levi M**, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999; **341**: 586-592 [PMID: 10451465 DOI: 10.1056/NEJM199908193410807]
- 5 **Dernaika TA**, Kinasewitz GT. Heparin in the treatment of severe sepsis: a new look at an old therapy. *Crit Care Med* 2008; **36**: 3098-3099 [PMID: 18941311 DOI: 10.1097/CCM.0b013e31818bdbc6]
- 6 **Kinasewitz GT**, Yan SB, Basson B, Comp P, Russell JA, Cariou A, Um SL, Utterback B, Laterre PF, Dhainaut JF. Universal changes in biomarkers of coagulation and inflammation occur in patients with severe sepsis, regardless of causative micro-organism [ISRCTN74215569]. *Crit Care* 2004; **8**: R82-R90 [PMID: 15025782 DOI: 10.1186/cc2459]
- 7 **Opal SM**. Therapeutic rationale for antithrombin III in sepsis. *Crit Care Med* 2000; **28**: S34-S37 [PMID: 11007195 DOI: 10.1097/00003246-200009001-00008]
- 8 **Fuchs TA**, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, Weinrauch Y, Brinkmann V, Zychlinsky A. Novel cell death program leads to neutrophil extracellular traps. *J Cell Biol* 2007; **176**: 231-241 [PMID: 17210947 DOI: 10.1083/jcb.200606027]
- 9 **Delvaeye M**, Conway EM. Coagulation and innate immune responses: can we view them separately? *Blood* 2009; **114**: 2367-2374 [PMID: 19584396 DOI: 10.1182/blood-2009-05-199208]
- 10 **Hunt BJ**. Bleeding and coagulopathies in critical care. *N Engl J Med* 2014; **370**: 847-859 [PMID: 24571757 DOI: 10.1056/NEJMra1208626]
- 11 **Engelmann B**, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol* 2013; **13**: 34-45 [PMID: 23222502 DOI: 10.1038/nri3345]
- 12 **Saadi S**, Holzknecht RA, Patte CP, Stern DM, Platt JL. Complement-mediated regulation of tissue factor activity in endothelium. *J Exp Med* 1995; **182**: 1807-1814 [PMID: 7500026 DOI: 10.1084/jem.182.6.1807]
- 13 **Semeraro N**, Colucci M. Tissue factor in health and disease. *Thromb Haemost* 1997; **78**: 759-764 [PMID: 9198252]
- 14 **Hack CE**. Tissue factor pathway of coagulation in sepsis. *Crit Care Med* 2000; **28**: S25-S30 [PMID: 11007193 DOI: 10.1097/00003246-200009001-00006]
- 15 **Rittirsch D**, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol* 2008; **8**: 776-787 [PMID: 18802444 DOI: 10.1038/nri2402]
- 16 **Iba T**, Kidokoro A. High-dose antithrombin therapy for sepsis: mechanisms of action. *Shock* 2002; **18**: 389-394 [PMID: 12412615 DOI: 10.1097/00024382-200211000-00001]
- 17 **Coughlan AF**, Hau H, Dunlop LC, Berndt MC, Hancock WW. P-selectin and platelet-activating factor mediate initial endotoxin-induced neutropenia. *J Exp Med* 1994; **179**: 329-334 [PMID: 7505802 DOI: 10.1084/jem.179.1.329]
- 18 **Duensing TD**, Wing JS, van Putten JP. Sulfated polysaccharide-directed recruitment of mammalian host proteins: a novel strategy in microbial pathogenesis. *Infect Immun* 1999; **67**: 4463-4468 [PMID: 10456887]
- 19 **Esmon CT**. Inflammation and the activated protein C anticoagulant pathway. *Semin Thromb Hemost* 2006; **32** Suppl 1: 49-60 [PMID: 16673266 DOI: 10.1055/s-2006-939554]
- 20 **Taylor FB**, Wada H, Kinasewitz G. Description of compensated and uncompensated disseminated intravascular coagulation (DIC) responses (non-overt and overt DIC) in baboon models of intravenous and intraperitoneal *Escherichia coli* sepsis and in the human model of endotoxemia: toward a better definition of DIC. *Crit Care Med* 2000; **28**: S12-S19 [PMID: 11007191 DOI: 10.1097/00003246-200009001-00004]

- 21 **Ramani V**, Madhusoodhanan R, Kosanke S, Awasthi S. A TLR4-interacting SPA4 peptide inhibits LPS-induced lung inflammation. *Innate Immun* 2013; **19**: 596-610 [PMID: 23475791 DOI: 10.1177/1753425912474851]
- 22 **Clark SR**, Ma AC, Tavener SA, McDonald B, Goodarzi Z, Kelly MM, Patel KD, Chakrabarti S, McAvoy E, Sinclair GD, Keys EM, Allen-Vercoe E, Devinney R, Doig CJ, Green FH, Kubes P. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. *Nat Med* 2007; **13**: 463-469 [PMID: 17384648 DOI: 10.1038/nm1565]
- 23 **Markiewski MM**, DeAngelis RA, Lambris JD. Complexity of complement activation in sepsis. *J Cell Mol Med* 2008; **12**: 2245-2254 [PMID: 18798865 DOI: 10.1111/j.1582-4934.2008.00504.x]
- 24 **Markiewski MM**, Nilsson B, Ekdahl KN, Mollnes TE, Lambris JD. Complement and coagulation: strangers or partners in crime? *Trends Immunol* 2007; **28**: 184-192 [PMID: 17336159 DOI: 10.1016/j.it.2007.02.006]
- 25 **Ward PA**. The dark side of C5a in sepsis. *Nat Rev Immunol* 2004; **4**: 133-142 [PMID: 15040586 DOI: 10.1038/nri1269]
- 26 **Wada H**, Asakura H, Okamoto K, Iba T, Uchiyama T, Kawasugi K, Koga S, Mayumi T, Koike K, Gando S, Kushimoto S, Seki Y, Madoiwa S, Maruyama I, Yoshioka A. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. *Thromb Res* 2010; **125**: 6-11 [PMID: 19782389 DOI: 10.1016/j.thromres.2009.08.017]
- 27 **Warren BL**, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Péntes I, Kübler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286**: 1869-1878 [PMID: 11597289 DOI: 10.1001/jama.286.15.1869]
- 28 **Wiedermann CJ**, Kaneider NC. A systematic review of antithrombin concentrate use in patients with disseminated intravascular coagulation of severe sepsis. *Blood Coagul Fibrinolysis* 2006; **17**: 521-526 [PMID: 16988545 DOI: 10.1097/01.mbc.0000245302.18010.40]
- 29 **Gando S**, Saitoh D, Ishikura H, Ueyama M, Otomo Y, Oda S, Kushimoto S, Tanjoh K, Mayumi T, Ikeda T, Iba T, Eguchi Y, Okamoto K, Ogura H, Koseki K, Sakamoto Y, Takayama Y, Shirai K, Takasu O, Inoue Y, Mashiko K, Tsubota T, Endo S. A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. *Crit Care* 2013; **17**: R297 [PMID: 24342495 DOI: 10.1186/cc13163]
- 30 **Tagami T**, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: an observational nationwide study. *J Thromb Haemost* 2014; **12**: 1470-1479 [PMID: 24943516]
- 31 **Xu J**, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, Taylor FB, Esmon NL, Lupu F, Esmon CT. Extracellular histones are major mediators of death in sepsis. *Nat Med* 2009; **15**: 1318-1321 [PMID: 19855397 DOI: 10.1038/nm.2053]
- 32 **Bouwens EA**, Stavenhagen F, Mosnier LO. Mechanisms of anticoagulant and cytoprotective actions of the protein C pathway. *J Thromb Haemost* 2013; **11** Suppl 1: 242-253 [PMID: 23809128]
- 33 **Bernard GR**, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709 [PMID: 11236773 DOI: 10.1056/NEJM200103083441001]
- 34 **Dhainaut JF**, Yan SB, Joyce DE, Pettit V, Basson B, Brandt JT, Sundin DP, Levi M. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004; **2**: 1924-1933 [PMID: 15550023 DOI: 10.1111/j.1538-7836.2004.00955.x]
- 35 **Vincent JL**, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; **33**: 2266-2277 [PMID: 16215381 DOI: 10.1097/01.CCM.0000181729.46010.83]
- 36 **Abraham E**, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, François B, Guy JS, Brückmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; **353**: 1332-1341 [PMID: 16192478 DOI: 10.1056/NEJMoa050935]
- 37 **Ranieri VM**, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; **366**: 2055-2064 [PMID: 22616830 DOI: 10.1056/NEJMoa1202290]
- 38 **Rimmer E**, Kumar A, Doucette S, Marshall J, Dial S, Gurka D, Dellinger RP, Sharma S, Penner C, Kramer A, Wood K, Ronald J, Kumar A, Turgeon AF, Houston DS, Zarychanski R. Activated protein C and septic shock: a propensity-matched cohort study*. *Crit Care Med* 2012; **40**: 2974-2981 [PMID: 22932397 DOI: 10.1097/CCM.0b013e31825fd6d9]
- 39 **Kalil AC**, LaRosa SP. Effectiveness and safety of drotrecogin alfa (activated) for severe sepsis: a meta-analysis and metaregression. *Lancet Infect Dis* 2012; **12**: 678-686 [PMID: 22809883 DOI: 10.1016/S1473-3099(12)70157-3]
- 40 **Aoki N**, Matsuda T, Saito H, Takatsuki K, Okajima K, Takahashi H, Takamatsu J, Asakura H, Ogawa N. A comparative double-blind randomized trial of activated protein C and unfractionated heparin in the treatment of disseminated intravascular coagulation. *Int J Hematol* 2002; **75**: 540-547 [PMID: 12095157 DOI: 10.1007/BF02982120]
- 41 **Ito T**, Kawahara K, Okamoto K, Yamada S, Yasuda M, Imaizumi H, Nawa Y, Meng X, Shrestha B, Hashiguchi T, Maruyama I. Proteolytic cleavage of high mobility group box 1 protein by thrombin-thrombomodulin complexes. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1825-1830 [PMID: 18599803 DOI: 10.1161/ATVBAHA.107.150631]
- 42 **Ito T**, Maruyama I. Thrombomodulin: protectorate God of the vasculature in thrombosis and inflammation. *J Thromb Haemost* 2011; **9** Suppl 1: 168-173 [PMID: 21781252]
- 43 **Saito H**, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, Ohno R, Hirayama A, Matsuda T, Asakura H, Nakashima M, Aoki N. Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; **5**: 31-41 [PMID: 17059423 DOI: 10.1111/j.1538-7836.2006.02267.x]
- 44 **Vincent JL**, Ramesh MK, Ernest D, LaRosa SP, Pacht J, Aikawa N, Hoste E, Levy H, Hirman J, Levi M, Daga M, Kutsogiannis DJ, Crowther M, Bernard GR, Devriendt J, Puigserver JV, Blanzaco DU, Esmon CT, Parrillo JE, Guzzi L, Henderson SJ, Pothirat C, Mehta P, Fareed J, Talwar D, Tsuruta K, Gorelick SJ, Osawa Y, Kaul I. A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. *Crit Care Med* 2013; **41**: 2069-2079 [PMID: 23979365 DOI: 10.1097/CCM.0b013e31828e9b03]
- 45 **Fuchs TA**, Bhandari AA, Wagner DD. Histones induce rapid and profound thrombocytopenia in mice. *Blood* 2011; **118**: 3708-3714 [PMID: 21700775 DOI: 10.1182/blood-2011-01-332676]
- 46 **Doshi SN**, Marmur JD. Evolving role of tissue factor and its pathway inhibitor. *Crit Care Med* 2002; **30**: S241-S250 [PMID: 12004243 DOI: 10.1097/00003246-200205001-00012]
- 47 **Jaimes F**, De La Rosa G, Morales C, Fortich F, Arango C, Aguirre D, Muñoz A. Unfractionated heparin for treatment of sepsis: A randomized clinical trial (The HETRASE Study). *Crit Care Med* 2009; **37**: 1185-1196 [PMID: 19242322 DOI: 10.1097/CCM.0b013e31819c06bc]
- 48 **Creasey AA**, Reinhart K. Tissue factor pathway inhibitor activity in severe sepsis. *Crit Care Med* 2001; **29**: S126-S129 [PMID: 11445747 DOI: 10.1097/00003246-200107001-00038]
- 49 **Abraham E**, Reinhart K, Svoboda P, Seibert A, Olthoff D,

- Dal Nogare A, Postier R, Hempelmann G, Butler T, Martin E, Zwingelstein C, Percell S, Shu V, Leighton A, Creasey AA. Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: a multicenter, randomized, placebo-controlled, single-blind, dose escalation study. *Crit Care Med* 2001; **29**: 2081-2089 [PMID: 11700399 DOI: 10.1097/00003246-200111000-00007]
- 50 **Abraham E**, Reinhart K, Opal S, Demeyer I, Doig C, Rodriguez AL, Beale R, Svoboda P, Laterre PF, Simon S, Light B, Spapen H, Stone J, Seibert A, Peckelsen C, De Deyne C, Postier R, Pettilä V, Artigas A, Percell SR, Shu V, Zwingelstein C, Tobias J, Poole L, Stolzenbach JC, Creasey AA. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003; **290**: 238-247 [PMID: 12851279 DOI: 10.1001/jama.290.2.238]
- 51 **Laterre PF**, Opal SM, Abraham E, LaRosa SP, Creasey AA, Xie F, Poole L, Wunderink RG. A clinical evaluation committee assessment of recombinant human tissue factor pathway inhibitor (tifacogin) in patients with severe community-acquired pneumonia. *Crit Care* 2009; **13**: R36 [PMID: 19284881 DOI: 10.1186/cc7747]
- 52 **Wunderink RG**, Laterre PF, Francois B, Perrotin D, Artigas A, Vidal LO, Lobo SM, Juan JS, Hwang SC, Dugernier T, LaRosa S, Wittebole X, Dhainaut JF, Doig C, Mendelson MH, Zwingelstein C, Su G, Opal S. Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2011; **183**: 1561-1568 [PMID: 21297074 DOI: 10.1164/rccm.201007-1167OC]
- 53 **Kidokoro A**, Iba T, Fukunaga M, Yagi Y. Alterations in coagulation and fibrinolysis during sepsis. *Shock* 1996; **5**: 223-228 [PMID: 8696988 DOI: 10.1097/00024382-199603000-00010]

P- Reviewer: Bugaj AM, Feltracco P, Owczarek D **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ



Fluid and electrolyte overload in critically ill patients: An overview

Bruno Adler Maccagnan Pinheiro Besen, André Luiz Nunes Gobatto, Lívia Maria Garcia Melro, Alexandre Toledo Maciel, Marcelo Park

Bruno Adler Maccagnan Pinheiro Besen, André Luiz Nunes Gobatto, Lívia Maria Garcia Melro, Alexandre Toledo Maciel, Marcelo Park, Intensive Care Unit, Department of Medical Emergencies, Hospital das Clínicas, University of Sao Paulo Medical School, Sao Paulo 05403000, Brazil

André Luiz Nunes Gobatto, Alexandre Toledo Maciel, Imed Research Group, Intensive Care Unit, Hospital Sao Camilo Pompéia, Sao Paulo 05022-001 Brazil

Author contributions: Besen BAMP, Gobatto ALN, Melro LMG, Maciel AT and Park M all contributed to this paper and fulfill all authorship credits in accordance with the ICMJE guidelines.

Conflict-of-interest: The authors have no conflicts of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Bruno Adler Maccagnan Pinheiro Besen, MD, Intensive Care Unit, Department of Medical Emergencies, Hospital das Clínicas, University of Sao Paulo Medical School, Carvalho Aguiar street, 255, 6th Floor, Room 6040, Sao Paulo 05403000, Brazil. brunobesen@yahoo.com.br

Telephone: +55-11-26616457

Received: September 29, 2014

Peer-review started: October 2, 2014

First decision: November 14, 2014

Revised: December 24, 2014

Accepted: March 4, 2015

Article in press: March 5, 2015

Published online: May 4, 2015

protection from endogenous and exogenous substances, for the safe dilution of medications and as "maintenance" fluids. However, a large amount of evidence from the last decade has shown that fluids can have deleterious effects on several organ functions, both from excessive amounts of fluids and from their non-physiological electrolyte composition. Additionally, fluid prescription is more common in patients with systemic inflammatory response syndrome whose kidneys may have impaired mechanisms of electrolyte and free water excretion. These processes have been studied as separate entities (hypernatremia, hyperchloremic acidosis and progressive fluid accumulation) leading to worse outcomes in many clinical scenarios, including but not limited to acute kidney injury, worsening respiratory function, higher mortality and higher hospital and intensive care unit length-of-stays. In this review, we synthesize this evidence and describe this phenomenon as fluid and electrolyte overload with potentially deleterious effects. Finally, we propose a strategy to safely use fluids and thereafter wean patients from fluids, along with other caveats to be considered when dealing with fluids in the intensive care unit.

Key words: Fluid therapy; Critically Ill; Oliguria; Water-electrolyte balance; Central venous pressure; Resuscitation; Acute kidney injury; Diuretics; Multiple organ dysfunction syndrome; Systemic inflammatory response syndrome

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Fluids are a cornerstone of the management of critically ill patients with systemic inflammatory response syndrome who are at risk of multiple organ dysfunction syndrome. However, as with any therapy, fluids can be associated with harm, such as added or worsening organ dysfunctions. Therefore, patients should be weaned from fluids when possible, sometimes through an active de-resuscitation strategy.

Abstract

Fluids are considered the cornerstone of therapy for many shock states, particularly states that are associated with relative or absolute hypovolemia. Fluids are also commonly used for many other purposes, such as renal

Besen BAMP, Gobatto ALN, Melro LMG, Maciel AT, Park M. Fluid and electrolyte overload in critically ill patients: An overview. *World J Crit Care Med* 2015; 4(2): 116-129 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i2/116.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i2.116>

INTRODUCTION

Fluids have been widely used in critically ill patients to optimize hemodynamics^[1], to enhance renal protection from contrast^[2], globins^[3], and uric acid^[4], to offer caloric intake^[5] and as an adjunct for medication dilution^[6]. During the first hours of shock syndromes, isotonic fluids can stabilize arterial pressure and perfusion and are lifesaving at times. Furthermore, to reach physiological hemodynamic targets, a large amount of intravenous fluids may be required. Some fasting patients receive infusions of one to three liters of dextrose in water with added electrolytes, mainly sodium, chloride and potassium, to avoid hypoglycemia, dehydration and electrolyte deficiency. Renal protection in critically ill patients is of huge importance, and hyperhydration is frequently used to enhance urine output and to avoid renal tubular cell injury by the retention of toxic substances at high concentrations. Finally, many drugs require a large amount of fluids with electrolytes to be safely administered.

Fluids and electrolytes are responsible for a large amount of volume that is infused in critically ill patients and are commonly associated with reduced urine output and renal electrolyte excretion failure, particularly chloride-rich solutions. This combination is even more accentuated in the first hours of critical illness^[1,7] or in the presence of acute kidney injury (AKI)^[8-10]. Ultimately, the inadequate management of fluids and electrolytes in critically ill patients culminates in hydroelectrolytic overload, which causes physiological derangements and worse outcomes^[11]. This manuscript describes the mechanisms, pathophysiology, and potential consequences of fluid and electrolyte overload and provides a combined bedside approach to avoid it.

ELECTROLYTE OVERLOAD

Primary electrolytes in basic human physiology

Sodium and chloride are the main determinants of colloid osmotic forces in human plasma and interstitial space because they account for 80% of the osmolality of these fluids^[12]. Plasma non-permeable proteins attract positively charged ions and repel negatively charged ions, leading to a passive transmembrane distribution of anions to preserve plasma and interstitial space electroneutrality, known as the Gibbs-Donnan effect. A steady-state is achieved when the plasmatic osmolality is 1 mOsm/L greater than the interstitial space, and the capillary hydrostatic pressure opposes the osmotic movement of the water into the intravascular space^[13].

Even at a constant interstitial space osmolality, to maintain cell volume, the transport of osmotically active substances across the cell membrane (mainly sodium and potassium) counterbalances the intracellular osmotic forces imposed by high-molecular-weight anionic proteins (Double-Donnan effect)^[14].

One of the main roles of electrolytes and their homeostasis is the distribution of fluids throughout the human body. Colloid osmotic and hydrostatic pressures are the main forces influencing the fluid distribution between intravascular and interstitial spaces, whereas changes in intra or extracellular osmolality are in general followed by water movement and determine the changes in cell volume^[14].

Sodium overload

Sodium is the main cation of solutions infused into critically ill patients. The 0.9% saline solution has 154 mEq/L of sodium, that is, one liter of 0.9% saline infusion carries 3.4 g of sodium, which represents approximately eight 100 g packages of commercially available potato chips, a huge amount of the electrolyte^[15]. Nevertheless, sodium renal excretion is largely impaired in critically ill patients,^[10] particularly in patients with AKI^[8].

In a sample of septic patients, for instance, the mean isotonic fluid intake was 5000 mL during the first 24 h in the ICU, with a urine output of 2000 mL during the same period and a mean sodium urinary concentration of 55 mEq/L^[16]. In this casuistic, the total amount of sodium infused was 770 mEq in the 24 h period analyzed with a concomitant sodium excretion of 110 mEq, resulting in a positive fluid and sodium balance of 3000 mL and 660 mEq, respectively. Because of the large sodium distribution volume in adults (49 L to 70 kg), the expected effect of the remaining 660 mEq of sodium and 3000 mL of water in patients with a pre-infusion sodium concentration of 145 mEq/L is approximately 4.0 mEq/L^[17]. Notably, patients with established kidney injuries were excluded from the Stelfox *et al.*^[18] study, and consequently the sodium overload effect in patients with AKI is expected to be even more striking. To exemplify this finding, Table 1 shows a water and electrolyte cumulative evolution of a mono-compartment mathematical model of a post-resuscitation phase with low urinary sodium and chloride, similar to the septic patients of Noritomi's study.

Other groups have also described resuscitation fluids as a contributing factor to ICU-acquired hypernatremia with a dose-response effect: the greater the saline infusion, the worse the hypernatremia condition^[19]. However, other sources of saline contribute to sodium loading in critically ill patients and may be a modifiable risk factor, such as normal saline used to dilute parenteral drugs and to keep catheters open^[20]. Finally, in Australia and New Zealand, a point-prevalence study demonstrated that sodium administration in excess

Table 1 Closed mono-compartment mathematical marginal model simulating the body water space of distribution

Variables	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Patient's resulting variables						
Na ⁺ (mEq/L)	140	142	148	151	146	144
Cl ⁻ (mEq/L)	100	108	114	117	113	111
Fluid balance (mL)	-	6000	0	800	800	0
Cumulative fluid balance (mL)	-	6000	6000	6800	7600	7600
Distribution water volume and electrolyte data						
Vd (L)	36	42	42	43	44	44
Total mass of Na ⁺ (mEq)	5040	5964	6216	6493	6424	6336
Total mass of Cl ⁻ (mEq)	3600	4536	4788	5031	4972	4884
Fluids output						
Diuresis (mL)	-	2000	1200	1200	1200	2000
Urinary Na ⁺ (mEq/L)	-	30	50	70	90	110
Urinary Cl ⁻ (mEq/L)	-	30	50	70	90	110
Fluids input						
Volume	6000	2000	2000	2000	2000	2000
Na ⁺ (mEq/L)	154	154	154	0	0	0
Cl ⁻ (mEq/L)	154	154	154	0	0	0

The main assumptions of this model are the absence of feces, sudoresis, renal replacement therapy, and the absence of Gibbs-Donnan effect. This patient was resuscitated with 4000 mL of 0.9% saline and received additional 2000 mL of 0.9 fluids during the Day 0. He received an amount of 0.9% saline during day 1 and day 2, afterwards the same 2000 mL of volume was infused without electrolytes due to hypernatremia. Vd: Denotes distribution volume.

of recommended daily requirements (*i.e.*, 1-2 mmol/kg) was fairly common, with the major sources being maintenance fluids (30.9%), fluid boluses (16.3%) and drug boluses (12.3%)^[21].

Hypernatremia is present at hospital admission and at ICU admission in 2% and 7% of patients, respectively^[22,23]. By contrast, up to 27% of patients in the ICU develop hypernatremia during their ICU stay^[18]. In a speculative view, this higher incidence of hypernatremia in critically ill patients might be explained by sodium overload. Critical illness related hypernatremia is associated with disease severity, kidney injury and dysfunction, mechanical ventilation and ICU length-of-stay^[18]. Finally, hypernatremia is associated with higher in-hospital mortality^[18,22,24,25] and it has been considered in several ICUs as a quality-of-care marker^[26,27]. Recently, a group also retrospectively noted that correcting this abnormality ultimately resulted in better survival^[28].

Chloride overload

Chloride is the main anion of fluids used in critical care settings, and its concentration is well correlated to the sodium concentration to maintain the electroneutrality of solutions^[29]. The 0.9% saline solution, Ringer's lactate solution, and Plasmalyte contain 154, 109 and 98 mEq/L of chloride, respectively^[15]. Because the serum chloride concentration is approximately 100 mEq/L, it is expected that a 0.9% saline infusion potentially increases the serum chloride concentration. In septic patients, Park *et al.*^[30] showed that 2000 ± 300 mL of a 0.9% saline infusion promptly resulted in a disproportionate elevation of serum chloride in comparison to the sodium concentration (Figure 1). Of note, this disproportionate elevation occurred in spite of equal chloride and sodium

concentrations in the 0.9% saline solution that was infused^[15,30].

The principle of the unequal chloride and sodium concentration elevations is based on the fact that the initial serum chloride concentration is lower than the initial sodium concentration. Therefore, the same infused amount in mEq/L of sodium and chloride is expected to have a greater effect on the ion with the lower serum concentration - in this case, chloride (Figure 2).

Kellum *et al.*^[31] demonstrated in a canine model of endotoxemia that only one-third of the post-volume infusion of chloride associated acidosis could be explained by exogenous chloride. The authors attributed this fact to an extravascular to intravascular chloride shift that was driven by differences in the transmembrane potential and the Gibbs-Donnan effect secondary to the fluid challenge. This same finding of chloride elevation was observed in humans with severe sepsis and septic shock^[16]. Therefore, one can expect an intrinsic chloride elevation in patients with systemic inflammation, which is amplified by a chloride-rich fluid infusion, such as the many previously described sources of normal saline that are infused in critically ill patients.

In addition to these sources of chloride, the renal excretion of chloride is also impaired, similarly to sodium excretion, during the initial phase of critical illness^[9,10], particularly in patients with AKI^[8]. The net result is a positive balance of chloride (Table 1), and an increased serum chloride concentration results in a hyperchloremic metabolic acidosis^[16,32]. This is also called "SID acidosis" and is not related to outcomes in mixed critically ill patients^[33]. However, specifically in septic patients, initial hyperchloremic acidosis is associated with a higher mortality^[16].

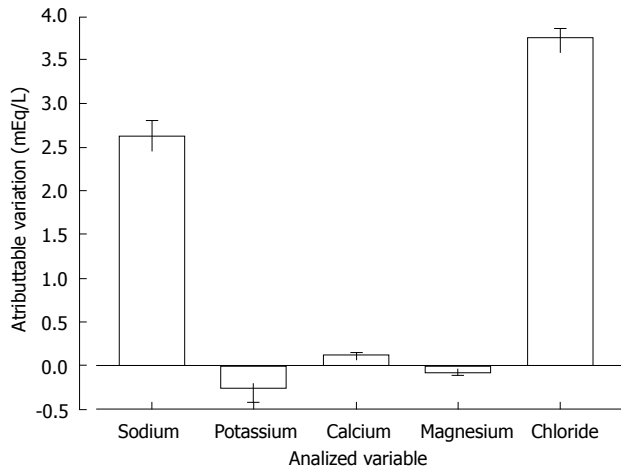


Figure 1 Variation of plasma electrolytes concentration immediately after 2000 ± 300 mL infusion of 0.9% saline in septic patients. Adapted from Park *et al*^[30].

Pathophysiology

Renal consequences: Electrolyte overload may have detrimental effects on renal function, particularly chloride overload. Animal studies suggest that chloride may influence renal blood flow (RBF), which is mediated primarily by its effects on afferent and intrarenal arterial vessels^[34,35]. In canine experiments, the renal infusion of solutions containing chloride, such as 0.9% saline or NH_4Cl , led to reductions in the total RBF and GFR in both denervated and *in situ* kidneys^[34]. In an animal model of sepsis, unbalanced solutions worsened sepsis-induced AKI^[36]. Other experiments confirmed that extracellular chloride is essential for contraction in renal afferent arterioles^[37,38]. In humans, an infusion of 2 L of 0.9% saline over 1 h was associated with a reduction in the RBF velocity and renal cortical tissue perfusion measured by magnetic resonance imaging (MRI); these changes were not observed after a similar infusion of a balanced crystalloid^[39]. Moreover, studies in healthy volunteers have shown a delayed urine output with saline compared to a balanced solution^[40].

An infusion of hypertonic solutions containing chloride into the renal artery causes a biphasic response in renal vascular resistance^[34]. Hyperosmolality leads to an abrupt renal vasodilatation and consequent increase in RBF. After 1-5 min, vasodilatation is reversed, and RBF and GFR decrease below pre-infusion levels. The second phase is absent in hypertonic solutions that do not contain chloride.

In vitro, the entry of chloride from elevated tubular chloride concentrations into epithelial renal cells causes the depolarization of the basolateral membrane^[41]. Increased NaCl concentrations in the macula densa stimulate ATP release, resulting in the extracellular formation of adenosine, which is involved in the signal transmission of the tubule-glomerular feedback response, increasing afferent arteriolar resistance and reducing GFR^[35,42].

Clinically, Yunos *et al*^[43] translated this experimental

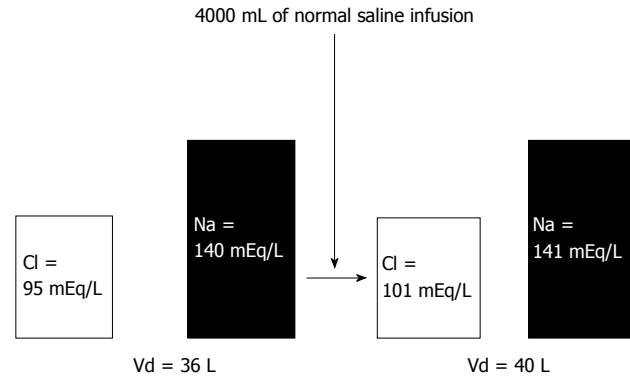


Figure 2 A monocompartmental model of intravascular 0.9% saline infusion, simulating the extracellular volume modification. To the initial distribution volume (Vd) = 36 L (approximately 60% of body mass of 60 kg), the total AMMOUNT of Cl^- and Na^+ were 3420 and 5040 mEq respectively. The infusion of 4000 mL of 0.9% saline results in additional 616 mEq of Cl^- and Na^+ to the total QUANTITY of extracellular electrolytes, that is, 4036 and 5656 mEq of Cl^- and Na^+ respectively. The new total AMMOUNT of electrolytes are distributed in a new Vd of 40 (36 + 4) liters, resulting in the new concentrations, where the chloride elevation was more striking than the sodium elevation.

knowledge to a large population of critically ill patients in a prospective open-label sequential period pilot study. After a control period and a wash-out phase, the use of chloride-rich intravenous fluids was restricted; this resulted in decreased chloride administration (694 to 496 mmol/patient) and led to better renal outcomes even after adjustment for covariates, including less high-severity AKI [OR = 0.52 (95%CI: 0.37-0.75); $P < 0.001$] and the reduced use of renal replacement therapy [OR = 0.52 (95%CI: 0.33-0.81); $P = 0.004$]^[43].

Acid-base consequences: Large volume resuscitation is commonly required in patients with sepsis and trauma. These patients may receive crystalloid infusions of many times their plasma volumes. Because the chloride concentration in 0.9% saline is approximately 50% higher than the plasma values, the chloride load associated with these volumes is significant. As previously described in this review, the chloride load associated with normal saline, which is a solution with a strong ion difference (SID) of 0, may be one of the main determinants of acidosis induced by fluids, along with chloride shifts that may occur in patients with sepsis (and other inflammatory states) and the Gibbs-Donnan effect after fluid challenges. These chloride loads and shifts interact with the patient's renal function, leading to both more AKI and subsequently lower chloride excretion, which might affect the kidney's recovery.

In surgical patients, when 0.9% saline was used as the primary intraoperative solution, significantly more acidosis was observed on completion of the surgery. These patients required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and were associated with the use of larger amounts of blood products^[44]. In another trial, a 0.9% saline infusion was compared to a balanced electrolyte and glucose solution. Two-thirds of the patients in the 0.9% saline

group but none of the patients in the balanced fluid group developed hyperchloremic metabolic acidosis, and the hyperchloremic acidosis was associated with reduced gastric mucosal perfusion on gastric tonometry^[45].

Although the effects of chloride are well studied, little is known about the potential contributions of sodium to the metabolic acid-base state. In a sample of 51 critically ill patients, a rise in serum sodium levels during the development of hyponatremia was accompanied by an increasing pH, serum bicarbonate, and standard base excess, and consequently metabolic alkalosis^[46]. In addition, the development of metabolic alkalosis correlated with the SID but not with the absolute serum sodium concentrations, indicating that the increase in the serum sodium-to-chloride ratio led to the development of metabolic alkalosis^[47].

Inflammatory response: Fluid and electrolyte overload may also influence cytokine production and the inflammatory response. In an animal model of hyperchloremic acidosis induced by dilute HCl infusion, moderate (SBE, - 5 to - 10) and severe (SBE, - 10 to - 15) acidosis significantly increased cytokine expression in a dose-dependent fashion in normotensive septic rats^[48]. These results are consistent with *in vitro* studies showing that HCl influences cytokine production in LPS-stimulated cells^[49], and pH interferes in nitric oxide^[50] and tumor necrosis- α production^[51] by macrophages in cell models. Interestingly, acidosis etiology may determine the inflammatory response pattern. Hyperchloremic acidosis is essentially pro-inflammatory as assessed by the increased NO release and the IL-6-to-IL-10 ratio, whereas lactic acidosis is associated with an anti-inflammatory pattern^[49].

Hemodynamic consequences: Chloride overload and its consequent hyperchloremic acidosis may have direct and independent deleterious effects on hemodynamics and survival. In an endotoxic shock model in rats, moderate and severe acidosis that was generated by HCl infusion induced a significant drop in blood pressure. This change in blood pressure was correlated with increases in plasma chloride concentrations and to a lesser degree with a decrease in pH^[52]. Furthermore, saline solution resuscitation was associated with a significantly shorter survival time compared to a balanced electrolyte solution containing starch in a similar animal model. Survival time was negatively correlated with both the decrease in pH and the increase in serum chloride following the initial resuscitation. The decrease in pH appeared to have been brought on by changes in chloride, lactate, and PaCO₂. However, lactate values were not different between the groups, and the changes in PaCO₂ were not correlated with survival time. Thus, hyperchloremic acidosis, rather than acidosis in general, was strongly and independently associated with early mortality in these animals^[53].

FLUID OVERLOAD

Pathophysiology

The renal compartment syndrome: The human body is composed of different organ systems. Lungs are, perhaps, the most affected organs by fluid overload, followed by encapsulated organs such as the kidneys. Experimental and clinical evidence from more than 30 years ago links the development of renal edema with oliguria and the perpetuation of ischemic AKI^[54]. This could be explained by reduced perfusion pressure through the kidneys as a result of higher central venous pressure, which has been better described in the context of cardiorenal syndromes^[55,56]. In addition to heart failure, patients with systemic inflammatory response syndrome (SIRS) may also develop interstitial edema and subsequently increases in interstitial pressure, leading to lower perfusion pressure, particularly in encapsulated organs such as the kidney^[57].

In animal models, Burnett *et al.*^[58] also demonstrated that an increase in renal venous pressure associated with volume expansion led to higher interstitial pressures and decreased sodium excretion in association with a decreased RBF and glomerular filtration rate. Recently, Cruces *et al.*^[59] experimentally described a model that provided even more support of the existence of a renal compartment. In their work, pressure had a nonlinear dependence on volume in the intact kidney, whereas the decapsulated kidney followed a linear pressure-volume curve, thus corroborating the hypothesis that kidney hypoperfusion might be explained by a reduced perfusion pressure. Clinical evidence supporting the role of interstitial edema to worse kidney outcomes will be discussed later in this review.

Pulmonary consequences: Derangements in the capillary permeability, which occurs in SIRS, combined with an increased hydrostatic pressure, as induced by aggressive fluid resuscitation, results in major interstitial edema that can lead to important clinical consequences.

Fluid overload increases hydrostatic pressure, leading to fluid accumulation in the lungs. Studies in mice have shown that the leakage occurs in the bronchiole, and the backflow of fluids leads to alveolar edema^[60]. There is a reabsorption of fluids in the interstitial space and, because the accumulated fluids are drained across the lymphatic vessels to the thoracic duct and superior vena cava, alterations in systemic venous pressure, which occurs during fluid overload, result in impaired lymphatic drainage and consequently pulmonary edema^[61], leading to a gas exchange impairment.

The high hydrostatic pressure not only causes fluid leakage but also generates mechanical stress injury to capillary walls, leading to the impairment of the mechanisms of fluid reabsorption^[62] and alveolo-capillary barrier damage^[63,64]. This damage causes

ultrastructural changes in the capillary, altering permeability to proteins and activating the inflammatory response^[65], which compromises gas exchange^[66].

Hypoxemia resulting from impaired gas exchange leads to lung regional blood flow redistribution. As demonstrated by Ruff *et al.*^[67], fluid overload leads to an inversion of the pulmonary perfusion pattern, with decreased blood flow to the pulmonary dependent regions and increased blood flow to the non-dependent regions, most likely because of hypoxic vasoconstriction.

The clinical features of pulmonary edema are not restricted to oxygenation but are a result of decreased pulmonary ventilation as well. In 1922, Drinker had described a tidal volume reduction of 40%-70% in an induced pulmonary edema animal model^[68], and a subsequent study has shown that a negative fluid balance strategy improved lung compliance and arterial oxygenation^[69].

Considering Starling's equation in which pulmonary edema is a result of colloid osmotic and hydrostatic forces, one approach to this clinical problem is to lower filling pressures. Despite concerns regarding lowering cardiac output and oxygen delivery, current evidence shows that a conservative fluid strategy improves the oxygenation index and number of ventilation-free days without compromising hemodynamics or other organ functions^[11,70].

Other organ consequences: Other organs might be affected by fluid overload in addition to the lungs and kidneys. Worse outcomes of the skin and the recovery of soft tissue wounds after surgery have been described, and the trial of Brandstrup *et al.*^[71] showed that a more conservative approach on fluids achieved better outcomes, particularly regarding surgical complications.

Gastrointestinal complications, such as ileum and anastomotic leakages, can also be increased because of interstitial edema associated with accumulated fluids during critical illness or major surgeries^[72]. This might lead to delays in the administration of nutritional needs and worsen the possibility of achieving an adequate enteral nutrition intake.

The liver is also an encapsulated organ, and interstitial edema could lead to a sort of compartment syndrome. In shock states, in addition to hypoperfusion, a high central venous pressure is required for the development of ischemic hepatitis^[73]. High venous pressures are usually secondary to a low cardiac output in patients with congestive heart failure, but it can also occur in fluid overloaded patients with SIRS who develop myocardial dysfunction.

From a broader perspective, abdominal compartment syndrome can be seen as another preventable complication of fluid overload. This syndrome would be an extreme situation regarding fluid overload states and can be either primary or secondary. In this case, fluid overload contributes to the development of abdominal compartment syndrome, leading to deleterious effects on many organ systems, including hemodynamic (as a result

of reduced venous return), renal (as a result of increased renal venous pressure) and even respiratory system mechanics (by reducing the thoracic wall compliance)^[74].

Other organ systems have more limited evidence associating fluid overload with worse outcomes. Although the brain could be considered an encapsulated organ, in general ICU patients whose blood-brain barrier is considered intact, fluid overload will most likely not lead to a significant cerebral edema that will develop into intracranial hypertension. However, it might be associated with an increased incidence of delirium^[75], which is associated with worse outcomes.

Acid-base water effect: Despite the effect of electrolytes on acid-base status, water itself might influence the acid-base status. Some experimental evidence from *in vitro* studies suggests that the dilution of plasma with distilled water changes many electrolyte concentrations, but because the ensuing proportions are maintained regarding the SID, PaCO₂ and weak anions, there is no significant difference in the pH^[76]. However, in a mathematical modeling approach validated thereafter with human plasma, Gattinoni *et al.*^[77] demonstrated that water itself, when in an open system, leads to acidosis, mainly because of the reaction of CO₂ with H₂O. The same group later described a possible rule that would regulate pH changes during crystalloid infusion, with interesting results. Mainly, the baseline [HCO₃⁻] values would dictate the pH response to a crystalloid solution whose (SID) would be the main determinant of the direction of the pH change^[78]. As an example, giving a patient both 0.9% saline [(SID) = 0] or dextrose in water [(SID) = 0] can lead to worsened acidemia, depending on the patient's renal function and pulmonary function to counteract these effects. However, 0.9% saline comes with an added cost, which is that of electrolyte overload, as we have discussed.

Observational evidence correlating fluid overload with worse outcomes

Fluid overload or cumulative fluid balances have been associated with worse outcomes in many scenarios, including in patients with sepsis^[79], cancer^[80], and surgical patients^[81], and during weaning from mechanical ventilation^[82] and at discharge from the ICU^[83].

A sub analysis of the VASST trial, which included patients with septic shock who were on vasopressors, reported that a positive fluid balance at both 12 h and 4 d after the onset of shock was associated with worse outcomes. Interestingly, the patients with CVP values below 8 mmHg at 12 h after septic shock onset had improved survival compared to patients with higher values of CVP^[79], which are recommended by the surviving sepsis campaign during the first hours of resuscitation^[84]. More provocative are the findings of Murphy *et al.*^[85], who studied a cohort of patients with septic shock who thereafter developed acute respiratory distress syndrome (ARDS), in which they hypothesized whether an adequate initial

fluid resuscitation strategy and a conservative late fluid management strategy were associated with improved survival^[85]. In this cohort, the patients who achieved both adequate initial fluid resuscitation and conservative late fluid management had the lowest mortality. Interestingly, the patients who achieved a conservative late fluid management but not adequate initial fluid resuscitation had lower mortality rates than those who achieved adequate initial fluid resuscitation but not conservative late fluid management. This appears to provide a lesson regarding this population: trying to optimize hemodynamics later in the course of the disease is most likely deleterious, whereas achieving negative fluid balances, *i.e.*, actively de-resuscitating patients even if the initial resuscitation was not deemed adequate, appears to be successful, particularly for patients with ARDS^[11]. In patients with ARDS, a large observational cohort also demonstrated that more positive fluid balances are associated with worse outcomes^[86].

In patients being weaned from mechanical ventilation, data demonstrate that a 24-h negative fluid balance on the day of the spontaneous breathing trial and a cumulative negative fluid balance were associated with better weaning outcomes^[82]. In another cohort of elderly patients, both negative fluid balances and decreasing values of central venous pressure were associated with better weaning outcomes^[87]. A higher cumulative fluid balance, even after ICU discharge, was also associated with worse outcomes during hospitalization^[83].

In patients with AKI, positive fluid balances have also been associated with worse outcomes. In a sub analysis of a European cohort of general ICU patients who developed AKI, a positive mean fluid balance was an independent risk factor for 60-d mortality^[88]. In a sub analysis of the RENAL study, the authors investigated the effect of fluid balance on the outcomes of patients with many different statistical approaches, and they consistently found an association between negative mean daily fluid balances and improved clinical outcomes^[89].

Many of these conditions in which fluid overload has been shown to be deleterious share a common feature: the presence of SIRS and the risk of multiple organ dysfunction syndrome, which can manifest clinically as shock along with AKI, ARDS and many other possible organ dysfunctions, septic or non-septic in origin^[90]. What remains to be established is whether fluid overload is only a biomarker^[91] that puts patients under an increased risk of death or an iatrogenic condition from critical care that should be considered in daily care and actively treated and avoided. This is a question to be answered with randomized controlled trials.

Randomized controlled trials correlating fluid overload with worse outcomes

Some randomized controlled trials in critically ill patients attempted to address whether a conservative

fluid management approach would result in better outcomes for patients instead of a liberal approach, testing the hypothesis that fluid overload is not only a biomarker but is also a modifiable risk factor for worsening organ dysfunctions and death. In each trial, the fluid-restrictive protocols were different; however, the greatest objective in all of the studies was to withdraw fluids from the patients and/or to avoid giving unnecessary fluids.

In patients admitted to an intensive care unit who required a pulmonary artery catheter, Mitchell *et al.*^[70] compared an extravascular lung-water based strategy against a wedge pressure-based strategy for the treatment of 101 patients. Regardless of the protocol used, in the extravascular lung-water based strategy, the cumulative fluid balance was 142 ± 3632 mL compared to 2239 ± 3695 mL in the other group. The conservative strategy led to better outcomes in this group although mortality was unchanged.

In patients undergoing high-risk colorectal surgery, Brandstrup *et al.*^[71] also tested another conservative strategy for fluid management during the perioperative state and achieved a significantly lower fluid balance in these patients, yielding a lower rate of complications after surgery, many of which included surgical wound repair and cardiopulmonary complications.

In the landmark FACTT trial, which included two different protocols for the fluid management of patients with ARDS, patients in the conservative group achieved a negative fluid balance throughout the course of the disease, whereas patients in the liberal group progressively accumulated more fluids during their ICU stay. The primary outcome (mortality) was not different between the groups. However, the conservative group achieved a higher number of ventilator-free days and ICU-free days but had less vasopressor free-days, along with a slight trend towards a lower dialysis requirement through day 60 ($P = 0.06$)^[11]. This trial demonstrated an interesting point: when using a conservative fluid management strategy, one will likely require vasopressors for a longer period but paradoxically at the benefit of being able to breathe without the ventilator sooner and being discharged from the ICU sooner. The cumulative fluid balance of both arms of the FACTT study is shown in Figure 3, as is the fluid balance of the ALVEOLI^[92] and ARMA^[93] studies about protective mechanical ventilation in ARDS patients.

Finally, during weaning from mechanical ventilation in a mixed ICU population, it has been demonstrated that a brain natriuretic peptide-driven strategy for fluid withdrawal resulted in more negative cumulative fluid balances [median, -180 (-2556; 2832) vs -2320 (-4735 to 738), $P < 0.001$], resulting in more ventilator-free days, although without impact on mortality^[94].

These trials, although conducted in different clinical scenarios, share an interesting feature. In the population of patients at risk of developing new organ failures (such as patients during high-risk surgery) or with ongoing organ failures (such as patients with ARDS) or even

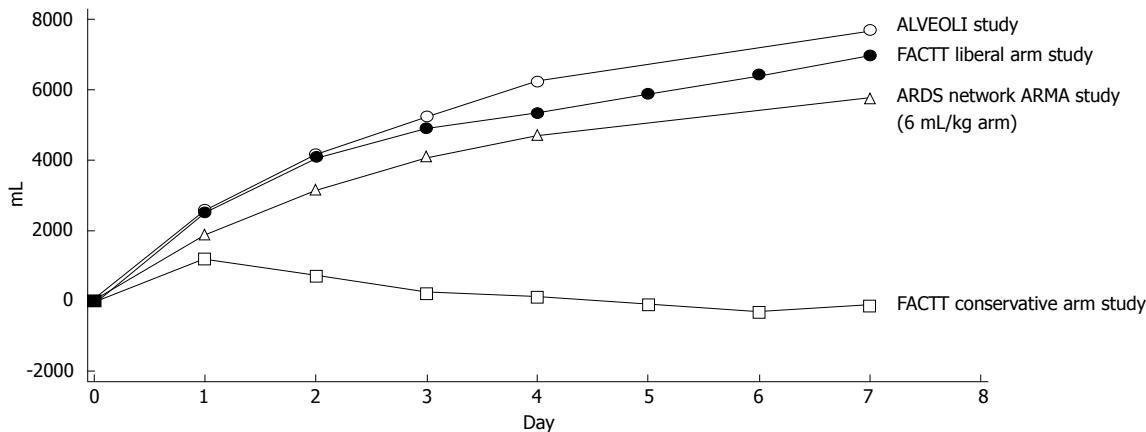


Figure 3 Cumulative fluid balances of the acute respiratory distress syndrome network group studies. The FACTT conservative fluid strategy arm returned to the neutral fluid balance within the first three days after randomization. The former strategy did not result in better survival, however patients were ventilated for less time and spent less time in the ICU in the conservative group. Adapted from Wiedemann *et al*^[11]. ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

during recovery of the critical illness, a conservative strategy led to better outcomes. Whether this can be extrapolated to all clinical scenarios remains to be answered.

The kidney paradox (oliguria worsened by fluid challenge)

Oliguria is usually considered a marker of decreased cardiac output, and a fluid challenge is often considered in an attempt to increase the cardiac preload and enhance cardiac output, which would ultimately enhance organ perfusion. However, after the optimization of hemodynamic parameters, some patients will still develop AKI and may have persistent oliguria on the ensuing days. Hence, after the first hours of resuscitation, oliguria should be interpreted as a marker of organ dysfunction but should not be seen as a marker of low cardiac output and does not necessarily indicate the need for volume expansion.

In this context of oliguria and a high risk of fluid overload, an added fluid challenge may worsen urine output and even renal function, as we have discussed previously in this review; most of the time, this will contribute to fluid and electrolyte overload. Clinically, Van Biesen *et al*^[95] demonstrated in a cohort of septic patients with AKI that additional fluid therapy failed to improve renal function, and other studies have shown an association between a positive fluid balance and worse outcomes in patients with AKI^[91], in addition to a decreased likelihood of renal recovery^[88,96]. Another implication of increasing cumulative fluid balances in this context is the potential underestimation of the diagnosis or severity of AKI because of an increased creatinine distribution volume^[97].

Therefore, this kidney paradox should be avoided in which clinicians attempt to enhance urinary output through repeated fluid challenges to avoid worsening kidney injury; these actions may in fact lead to more fluid accumulation and ultimately a worse outcome.

A BEDSIDE PATIENT-TAILORED APPROACH

To avoid potentially deleterious complications associated with fluid and electrolyte overload (Table 2), a patient-tailored approach is necessary to result in better outcomes for the individual patient. This will involve some aspects of fluid resuscitation, maintenance fluids, other sources of electrolytes and water and, ultimately, an active de-resuscitation strategy that may aim at the fluid balance and, if performed adequately will also remove the excessive loads of sodium and chloride. Here we describe how clinicians can address this situation at the bedside.

Judicious resuscitation

During the acute phase of resuscitation, fluids should be used judiciously to achieve an adequate perfusion. This encompasses four distinct aspects of fluid resuscitation: timing, type, amount and avoidance of the kidney paradox^[98].

Resuscitation with fluids should be performed during the appropriate timing for this action, which occurs during the onset of the injury (intra-operative states) or soon after it (first hours after septic shock, major surgery or other acute physiological insults)^[1]. There is no evidence that fluid resuscitation after these first moments will lead to better results. In fact, as we have discussed so far, the evidence points in the opposite direction.

In general, balanced solutions should be the fluids of choice in patients with shock states because they carry a lower chloride load, lead to less acid-base disturbances and most likely to better organ dysfunction outcomes, particularly for the kidneys, as shown in the study by Yunos *et al*^[43].

The proper amount of fluid for acute care resuscitation is another critical component of judicious resuscitation. A recently published cohort of septic patients from

Table 2 Potential complications of fluids and electrolytes overload

Organ system	Complication	Main modifiable risk factor	Pathophysiological mechanism
Central nervous system	Delirium	Hypernatremia	Excessive sodium load Kidneys inability to excrete excess sodium load
Renal/metabolic	Worse recovery of renal function	Cumulative fluid balance/higher CVP	Renal edema, reduced perfusion pressure
	Worsening acute kidney injury	Unbalanced solutions	Chloride-induced renal vasoconstriction
	Worsening acidemia	Unbalanced solutions	Solution SID relative to plasma SID Kidneys inability to excrete excess chloride load
Respiratory	Impaired gas exchange	Cumulative fluid balance/higher CVP/higher EVLW	Lung edema
	Altered pulmonar and chest wall mechanics		
	Increased work of breathing		
Gastrointestinal	Ileum	Cumulative fluid balance	Bowel edema
	Hepatic congestion	Higher CVP	Hepatic congestion
	Increased intra-abdominal pressure (may induce by itself more organ dysfunctions)	Cumulative fluid balance	Visceral edema (bowel, renal, etc.), ascites
Hemostasis	Increased bleeding	Unbalanced solutions	Acidemia secondary to chloride load
Wound healing	Impaired wound healing	Cumulative fluid balance	Local edema
Hemodynamics	Worse microcirculatory blood flow	Higher CVP	Reduced perfusion pressure

CVP: Central venous pressure; SID: Strong ion difference; EVLW: Extravascular lung water.

Australia and New Zealand, which yielded impressive mortality outcomes, demonstrated that patients received approximately 3 L of fluids during the first hours of resuscitation^[99]. Furthermore, in the recently published PROCESS trial, in patients who received more fluids (approximately 1 L more) in one of the three study arms, there were more cases of new onset renal failure than the usual care group^[7]. With this in mind, particularly in cases of septic shock, after an initial fluid challenge of 20-30 mL/kg, we favor an earlier use of vasopressors and the avoidance of repeated fluid expansion in patients with vasodilatory states, particularly in those with adequate perfusion parameters who are no longer fluid-responsive^[100].

Another issue to be considered is to avoid the “kidney paradox”. In oliguric patients, one should strongly consider avoiding repeated volume expansions after the first hours of resuscitation because this will most likely lead to higher filling pressures and more fluid accumulation despite a possibly increased urine output. In patients who further develop anuria, fluid challenges might be even more deleterious.

Acid-base monitoring during resuscitation

During the resuscitation phase of critical illness, in addition to usual hemodynamic monitoring, it is important to monitor potentially deleterious effects of fluids and electrolytes on the acid-base status. As previously discussed, both fluid composition and quantity can influence acid-base status^[98]. Through acid-base monitoring, one can identify at an earlier stage metabolic complications occurring during resuscitation. If possible, one should attempt to quantify which component of metabolic acidosis is worse during acute resuscitation because they carry different prognostic significances^[16].

Active de-resuscitation

After a judicious resuscitation strategy, active de-

resuscitation should be considered to avoid the deleterious effects of continuous fluid accumulation when the patient does not passively excrete the excess amount of water and electrolytes. This can be achieved both with diuretics, which have been shown to be safe in the context of AKI, or with an earlier indication of hemodialysis, as defended by some authors, when the former cannot control fluid overload^[101]. To achieve a safe withdrawal of fluids and electrolytes, some factors must be considered:

Fluid removal rate: either with dialysis or diuretics, the fluid removal rate should be titrated to the patient hemodynamic status to avoid underfilling during this phase^[102]. If tolerated, there will likely be no deleterious effects of fluid withdrawal, even in the presence of vasopressors or inotropic drugs.

Intermittent vs continuous infusion of diuretics: in critically ill patients, the continuous infusion of diuretics was not extensively studied. Better evidence from other clinical situations has not demonstrated any consistent advantage of one way of administering diuretics over another, except for higher doses of diuretics in intermittent therapy for the same fluid balance achievement compared to continuous infusion diuretic therapy^[103,104]. As long as a target diuresis is achieved, there will likely be no differences among these treatments.

Association of albumin to furosemide: although albumin was not associated with better outcomes in patients with septic shock^[105] or for fluid resuscitation in general ICU patients^[106], in patients with ARDS, a better hemodynamic tolerance during fluid withdrawal was achieved with the combination of albumin and furosemide^[107] and could be a useful adjunct during the active de-resuscitation phase.

Monitoring and treating metabolic complications: the use of diuretics is associated with more metabolic disturbances, including hypernatremia, hypokalemia and metabolic alkalosis^[11]. To counteract these disturbances,

we favor the use of acetazolamide if the patient develops metabolic alkalosis, thiazide diuretics and increases in free water reposition if hyponatremia ensues and the aggressive reposition of electrolytes to avoid extreme electrolyte disturbances. We refer the reader to the trial by Mekontso Dessap *et al.*^[94], which proposed a method to do this safely with a combination of diuretics.

Consideration for an earlier indication of renal replacement therapy in oliguria should be part of an active de-resuscitation strategy because some patients will develop stage III AKI^[108], will be unresponsive to diuretics and, during this process, will accumulate fluids progressively, which has been consistently shown to be associated with worse outcomes in this specific population^[88,89,96].

Although pulmonary edema is a common trigger for fluid withdrawal, it is a late and potentially deadly consequence of fluid overload. Hence, during this phase of active fluid withdrawal, some very simple monitoring strategies can be used.

Central venous pressure, although recently receiving discredit as a guide to fluid loading^[109], was used in the largest randomized controlled trial on conservative fluid strategies^[11]. In this regard, although there are many physiological states that can influence its isolated value, higher CVP values have been associated with worse outcomes in many conditions, including septic shock^[79], likely not only because of fluid overload but also because of the associated significant effect of heart dysfunction on its values. Therefore, it can be an adjunct for active de-resuscitation strategies, and a goal towards lower CVP values (e.g., down to < 4 mmHg in adequately perfused patients without vasopressors) is a simple way to monitor this strategy.

An even simpler solution is to focus on fluid balance. Although daily weights would potentially be better, these values are also prone to error when measuring patients on ICU beds^[110], and we believe that fluid balance, although imperfect, appears to be a simple bedside target of active de-resuscitation. Therefore, reaching even to negative fluid balances during the first days of critical illness onset and, as soon as possible, aiming at more negative fluid balances until reaching a cumulative fluid balance of approximately zero during the ICU stay appears to be a good approach.

In addition to active fluid withdrawal, one should avoid the unnecessary entrance of fluids and electrolytes in the form of electrolyte reposition, drugs dilution and as caloric intake on a daily basis because as we have previously discussed, these are important sources of sodium, chloride and water. In this regard, we favor using hypertonic glucose solutions if deemed necessary for minimum caloric intake (when the enteral route is not available for feeding) and the avoidance of maintenance fluids when there are no clinically relevant fluid losses (e.g., ileostomy). Finally, electrolytes, antimicrobials and other drugs should be diluted in the minimum necessary amount of fluids and preferentially in 5% dextrose in water^[20].

With all this evidence combined, it appears that a judicious initial fluid resuscitation followed by a conservative fluid management approach will lead to better outcomes in patients in many different shock states, including in patients with sepsis and patients with other causes of non-septic SIRS. As we have discussed, hyponatremia is associated with worse outcomes, along with hyperchloremic acidosis in some scenarios and also progressive cumulative fluid balances. Many of the studies in this regard examined these issues separately, whereas these may be different aspects of the same problem: that of fluid and electrolyte overload.

CONCLUSION

Although there are no adequate prospective experimentally designed studies that have shown that fluids are essential in the treatment of critically ill patients, fluids are used liberally among ICU patients, and fluid accumulation is very common throughout the course of a patient's ICU stay. In this review, we provided evidence of the potentially deleterious effects of fluids and electrolytes on many organ systems, how to monitor for these complications and how to manage this increasingly recognized clinical problem. Currently, we favor a more conservative approach regarding fluid management strategies in general ICU patients, although a randomized controlled trial addressing this issue is mandatory to shed light on this discussion, along with deeper mechanistic studies to understand the relative contributions of each component of fluid therapy.

REFERENCES

- 1 **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169 DOI: 10.1056/NEJMoa010307]
- 2 **Eisenberg RL**, Bank WO, Hedgcock MW. Renal failure after major angiography can be avoided with hydration. *AJR Am J Roentgenol* 1981; **136**: 859-861 [PMID: 6784516 DOI: 10.2214/ajr.136.5.859]
- 3 **Gunal AI**, Celiker H, Dogukan A, Ozalp G, Kirciman E, Simsekli H, Gunay I, Demircin M, Belhan O, Yildirim MA, Sever MS. Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. *J Am Soc Nephrol* 2004; **15**: 1862-1867 [PMID: 15213274 DOI: 10.1097/01.ASN.0000129336.09976.73]
- 4 **Davidson MB**, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 2004; **116**: 546-554 [PMID: 15063817 DOI: 10.1016/j.amjmed.2003.09.045]
- 5 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]
- 6 **Nemec K**, Kopelent-Frank H, Greif R. Standardization of infusion solutions to reduce the risk of incompatibility. *Am J Health Syst Pharm* 2008; **65**: 1648-1654 [PMID: 18714112 DOI: 10.2146/ajhp070471]
- 7 **Yealy DM**, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care

- for early septic shock. *N Engl J Med* 2014; **370**: 1683-1693 [PMID: 24635773 DOI: 10.1056/NEJMoa1401602]
- 8 **Maciel AT**, Park M, Macedo E. Physicochemical analysis of blood and urine in the course of acute kidney injury in critically ill patients: a prospective, observational study. *BMC Anesthesiol* 2013; **13**: 31 [PMID: 24112801 DOI: 10.1186/1471-2253-13-31]
- 9 **Maciel AT**, Park M. Urine assessment in the critically ill: a matter of both quantity and quality. *Rev Bras Ter Intensiva* 2013; **25**: 184-185 [PMID: 24213079 DOI: 10.5935/0103-507X.20130032]
- 10 **Maciel AT**, Park M, Macedo E. Urinary electrolyte monitoring in critically ill patients: a preliminary observational study. *Rev Bras Ter Intensiva* 2012; **24**: 236-245 [PMID: 23917824 DOI: 10.1590/S0103-507X2012000300006]
- 11 **National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network**; Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]
- 12 **Guyton AC**, Hall JE. The body fluid compartments: extracellular and intracellular fluids; interstitial fluid and edema. In: Guyton AC, Hall JE, editors. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: Saunders, 2000: 250-264
- 13 **Nguyen MK**, Kurtz I. Quantitative interrelationship between Gibbs-Donnan equilibrium, osmolality of body fluid compartments, and plasma water sodium concentration. *J Appl Physiol* (1985) 2006; **100**: 1293-1300 [PMID: 16357067 DOI: 10.1152/japplphysiol.01274.2005]
- 14 **Lang F**, Busch GL, Ritter M, Völkl H, Waldegger S, Gulbins E, Häussinger D. Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 1998; **78**: 247-306 [PMID: 9457175]
- 15 **Guidet B**, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, James M. A balanced view of balanced solutions. *Crit Care* 2010; **14**: 325 [PMID: 21067552 DOI: 10.1186/cc9230]
- 16 **Noritomi DT**, Soriano FG, Kellum JA, Cappi SB, Biselli PJ, Libório AB, Park M. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. *Crit Care Med* 2009; **37**: 2733-2739 [PMID: 19885998 DOI: 10.1097/CCM.0b013e3181a59165]
- 17 **Adrogué HJ**, Madias NE. Aiding fluid prescription for the dysnatremias. *Intensive Care Med* 1997; **23**: 309-316 [PMID: 9083234 DOI: 10.1007/s001340050333]
- 18 **Steffox HT**, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care* 2008; **12**: R162 [PMID: 19094227 DOI: 10.1186/cc7162]
- 19 **Van De Louw A**, Shaffer C, Schaefer E. Early intensive care unit-acquired hypernatremia in severe sepsis patients receiving 0.9% saline fluid resuscitation. *Acta Anaesthesiol Scand* 2014; **58**: 1007-1014 [PMID: 25039806 DOI: 10.1111/aas.12368]
- 20 **Choo WP**, Groeneveld AB, Driessen RH, Swart EL. Normal saline to dilute parenteral drugs and to keep catheters open is a major and preventable source of hypernatremia acquired in the intensive care unit. *J Crit Care* 2014; **29**: 390-394 [PMID: 24603000 DOI: 10.1016/j.jcrc.2014.01.025]
- 21 **Bihari S**, Peake SL, Seppelt I, Williams P, Bersten A; George Institute for Global Health; Australian and New Zealand Intensive Care Society Clinical Trials Group. Sodium administration in critically ill patients in Australia and New Zealand: a multicentre point prevalence study. *Crit Care Resusc* 2013; **15**: 294-300 [PMID: 24289511]
- 22 **Arampatzis S**, Frauchiger B, Fiedler GM, Leichtle AB, Buhl D, Schwarz C, Funk GC, Zimmermann H, Exadaktylos AK, Lindner G. Characteristics, symptoms, and outcome of severe dysnatremias present on hospital admission. *Am J Med* 2012; **125**: 1125.e1-1125.e7 [PMID: 22939097 DOI: 10.1016/j.amjmed.2012.04.041]
- 23 **Funk GC**, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, Metnitz PG. Incidence and prognosis of dysnatremias present on ICU admission. *Intensive Care Med* 2010; **36**: 304-311 [PMID: 19847398 DOI: 10.1007/s00134-009-1692-0]
- 24 **Lindner G**, Funk GC, Schwarz C, Kneidinger N, Kaider A, Schneeweiss B, Kramer L, Druml W. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis* 2007; **50**: 952-957 [PMID: 18037096 DOI: 10.1053/j.ajkd.2007.08.016]
- 25 **Vandergheynst F**, Sakr Y, Felleiter P, Hering R, Groeneveld J, Vanhems P, Taccone FS, Vincent JL. Incidence and prognosis of dysnatraemia in critically ill patients: analysis of a large prevalence study. *Eur J Clin Invest* 2013; **43**: 933-948 [PMID: 23869476 DOI: 10.1111/eci.12123]
- 26 **Lindner G**, Funk GC. Hypernatremia in critically ill patients. *J Crit Care* 2013; **28**: 216.e11-216.e20 [PMID: 22762930 DOI: 10.1016/j.jcrc.2012.05.001]
- 27 **Lindner G**. "Hypernatremia in the intensive care unit--an iatrogenic complication?". *J Crit Care* 2013; **28**: 214-215 [PMID: 23337488 DOI: 10.1016/j.jcrc.2012.11.017]
- 28 **Darmon M**, Pichon M, Schwebel C, Ruckly S, Adrie C, Haouache H, Azoulay E, Bouadma L, Clec'h C, Garrouste-Orgeas M, Souweine B, Goldgran-Toledano D, Khallil H, Argaud L, Dumenil AS, Jamali S, Allaouchiche B, Zeni F, Timsit JF. Influence of early dysnatremia correction on survival of critically ill patients. *Shock* 2014; **41**: 394-399 [PMID: 24667611 DOI: 10.1097/SHK.000000000000135]
- 29 **Berend K**, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? *Eur J Intern Med* 2012; **23**: 203-211 [PMID: 22385875 DOI: 10.1016/j.ejim.2011.11.013]
- 30 **Park M**, Calabrich A, Maciel A, Zampieri F, Taniguchi L, Souza C, Barboza C, Nassar Junior AP, Azevedo L. Physicochemical characterization of metabolic acidosis induced by normal saline resuscitation of patients with severe sepsis and septic shock. *Rev Bras Ter Intensiva* 2011; **23**: 176-182 [DOI: 10.1590/S0103-507X2011000200010]
- 31 **Kellum JA**, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock* 1998; **9**: 364-368 [PMID: 9617887 DOI: 10.1097/00024382-199805000-00009]
- 32 **Maciel AT**, Park M. Differences in acid-base behavior between intensive care unit survivors and nonsurvivors using both a physicochemical and a standard base excess approach: a prospective, observational study. *J Crit Care* 2009; **24**: 477-483 [PMID: 19327958 DOI: 10.1016/j.jcrc.2009.01.005]
- 33 **Boniatti MM**, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. *J Crit Care* 2011; **26**: 175-179 [PMID: 20619601 DOI: 10.1016/j.jcrc.2010.04.013]
- 34 **Wilcox CS**. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; **71**: 726-735 [PMID: 6826732 DOI: 10.1172/JCI10820]
- 35 **Imig JD**, Passmore JC, Anderson GL, Jimenez AE. Chloride alters renal blood flow autoregulation in deoxycorticosterone-treated rats. *J Lab Clin Med* 1993; **121**: 608-613 [PMID: 8454943]
- 36 **Zhou F**, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis*. *Crit Care Med* 2014; **42**: e270-e278 [PMID: 24335444 DOI: 10.1097/CCM.000000000000145]
- 37 **Jensen BL**, Ellekvist P, Skott O. Chloride is essential for contraction of afferent arterioles after agonists and potassium. *Am J Physiol* 1997; **272**: F389-F396 [PMID: 9087683]
- 38 **Hansen PB**, Jensen BL, Skott O. Chloride regulates afferent arteriolar contraction in response to depolarization. *Hypertension* 1998; **32**: 1066-1070 [PMID: 9856975 DOI: 10.1161/01.HYP.32.6.1066]
- 39 **Chowdhury AH**, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; **256**: 18-24 [PMID: 22580944 DOI: 10.1097/SLA.0b013e318256be72]
- 40 **Reid F**, Lobo DN, Williams RN, Rowlands BJ, Allison SP.

- (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci (Lond)* 2003; **104**: 17-24 [PMID: 12519083 DOI: 10.1042/CS20020202]
- 41 **Bell PD**, Lapointe JY, Cardinal J. Direct measurement of basolateral membrane potentials from cells of the macula densa. *Am J Physiol* 1989; **257**: F463-F468 [PMID: 2782426]
 - 42 **Ren Y**, Garvin JL, Liu R, Carretero OA. Role of macula densa adenosine triphosphate (ATP) in tubuloglomerular feedback. *Kidney Int* 2004; **66**: 1479-1485 [PMID: 15458441 DOI: 10.1111/j.1523-1755.2004.00911.x]
 - 43 **Yunos NM**, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566-1572 [PMID: 23073953 DOI: 10.1001/jama.2012.13356]
 - 44 **Waters JH**, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 2001; **93**: 817-822 [PMID: 11574339 DOI: 10.1097/00000539-200110000-00004]
 - 45 **Wilkes NJ**, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* 2001; **93**: 811-816 [PMID: 11574338 DOI: 10.1097/00000539-200110000-00003]
 - 46 **Lindner G**, Schwarz C, Grüssing H, Kneidinger N, Fazekas A, Funk GC. Rising serum sodium levels are associated with a concurrent development of metabolic alkalosis in critically ill patients. *Intensive Care Med* 2013; **39**: 399-405 [PMID: 23160772 DOI: 10.1007/s00134-012-2753-3]
 - 47 **Hofmann-Kiefer KF**, Chappell D, Jacob M, Schülke A, Conzen P, Rehm M. [Hypernatremic alkalosis. Possible counterpart of hyperchloremic acidosis in intensive care patients?]. *Anaesthesist* 2009; **58**: 1210-1215 [PMID: 19911108 DOI: 10.1007/s00101-009-1640-y]
 - 48 **Kellum JA**, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. *Chest* 2006; **130**: 962-967 [PMID: 17035425 DOI: 10.1378/chest.130.4.962]
 - 49 **Kellum JA**, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol* 2004; **286**: R686-R692 [PMID: 14695114 DOI: 10.1152/ajpregu.00564.2003]
 - 50 **Belloq A**, Suberville S, Philippe C, Bertrand F, Perez J, Fouqueray B, Cherqui G, Baud L. Low environmental pH is responsible for the induction of nitric-oxide synthase in macrophages. Evidence for involvement of nuclear factor-kappaB activation. *J Biol Chem* 1998; **273**: 5086-5092 [PMID: 9478960 DOI: 10.1074/jbc.273.9.5086]
 - 51 **Heming TA**, Davé SK, Tuazon DM, Chopra AK, Peterson JW, Bidani A. Effects of extracellular pH on tumour necrosis factor- α production by resident alveolar macrophages. *Clin Sci (Lond)* 2001; **101**: 267-274 [PMID: 11524044 DOI: 10.1042/CS20010139]
 - 52 **Kellum JA**, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest* 2004; **125**: 243-248 [PMID: 14718447 DOI: 10.1378/chest.125.1.243]
 - 53 **Kellum JA**. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med* 2002; **30**: 300-305 [PMID: 11889298 DOI: 10.1097/00003246-200202000-0-00006]
 - 54 **Stone HH**, Fulenwider JT. Renal decapsulation in the prevention of post-ischemic oliguria. *Ann Surg* 1977; **186**: 343-355 [PMID: 407854 DOI: 10.1097/0000658-197709000-00012]
 - 55 **Bock JS**, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; **121**: 2592-2600 [PMID: 20547939 DOI: 10.1161/CIRCULATIONAHA.109.886473]
 - 56 **Damman K**, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; **53**: 582-588 [PMID: 19215832 DOI: 10.1016/j.jacc.2008.08.080]
 - 57 **Legrand M**, Dupuis C, Simon C, Gayat E, Mateo J, Lukasiewicz AC, Payen D. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. *Crit Care* 2013; **17**: R278 [PMID: 24289206 DOI: 10.1186/cc13133]
 - 58 **Burnett JC**, Knox FG. Renal interstitial pressure and sodium excretion during renal vein constriction. *Am J Physiol* 1980; **238**: F279-F282 [PMID: 7377299]
 - 59 **Cruces P**, Salas C, Lillo P, Salomon T, Lillo F, Hurtado DE. The renal compartment: a hydraulic view. *Intensive Care Medicine* 2014; **2**: 26 [DOI: 10.1186/s40635-014-0026-x]
 - 60 **Yoneda K**. Anatomic pathway of fluid leakage in fluid-overload pulmonary edema in mice. *Am J Pathol* 1980; **101**: 7-16 [PMID: 7446703]
 - 61 **Laine GA**, Allen SJ, Katz J, Gabel JC, Drake RE. Effect of systemic venous pressure elevation on lymph flow and lung edema formation. *J Appl Physiol* (1985) 1986; **61**: 1634-1638 [PMID: 3781976]
 - 62 **West JB**, Mathieu-Costello O. Vulnerability of pulmonary capillaries in heart disease. *Circulation* 1995; **92**: 622-631 [PMID: 7634477 DOI: 10.1161/01.CIR.92.3.622]
 - 63 **West JB**. Invited review: pulmonary capillary stress failure. *J Appl Physiol* (1985) 2000; **89**: 2483-2489; discussion 2497 [PMID: 11090605]
 - 64 **Tsukimoto K**, Mathieu-Costello O, Prediletto R, Elliott AR, West JB. Ultrastructural appearances of pulmonary capillaries at high transmural pressures. *J Appl Physiol* (1985) 1991; **71**: 573-582 [PMID: 1718936]
 - 65 **De Pasquale CG**, Arnolda LF, Doyle IR, Grant RL, Aylward PE, Bersten AD. Prolonged alveolocapillary barrier damage after acute cardiogenic pulmonary edema. *Crit Care Med* 2003; **31**: 1060-1067 [PMID: 12682473 DOI: 10.1097/01.CCM.0000059649.31659.22]
 - 66 **Guazzi M**. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest* 2003; **124**: 1090-1102 [PMID: 12970042 DOI: 10.1378/chest.124.3.1090]
 - 67 **Ruff F**, Caubarrere I, Salem A, Dubois F, Duroux P. [Regional distribution of pulmonary perfusion during fluid overload in man]. *Ann Anesthesiol Fr* 1975; **16** Spec No 2-3: 164-168 [PMID: 9861]
 - 68 **Drinker CK**, Peabody FW, Blumgart HL. The effect of pulmonary congestion on the on the ventilation of the lungs. *J Exp Med* 1922; **35**: 77-95 [PMID: 19868589 DOI: 10.1084/jem.35.1.77]
 - 69 **Bone RC**. Treatment of adult respiratory distress syndrome with diuretics, dialysis, and positive end-expiratory pressure. *Crit Care Med* 1978; **6**: 136-139 [PMID: 350486 DOI: 10.1097/00003246-197805000-00002]
 - 70 **Mitchell JP**, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; **145**: 990-998 [PMID: 1586077 DOI: 10.1164/ajrccm/145.5.990]
 - 71 **Brandstrup B**, Tønnesen H, Beier-Holgersen R, Hjortso E, Ørting H, Lindorff-Larsen K, Rasmussen MS, Lannig C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilmann D, Christensen AM, Graungaard B, Pott F. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641-648 [PMID: 14578723 DOI: 10.1097/01.sla.0000094387.50865.23]
 - 72 **Macafee DA**, Allison SP, Lobo DN. Some interactions between gastrointestinal function and fluid and electrolyte homeostasis. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 197-203 [PMID: 15716800 DOI: 10.1097/00075197-200503000-00015]
 - 73 **Seeto RK**, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. *Am J Med* 2000; **109**: 109-113 [PMID: 10967151 DOI: 10.1016/S0002-9343(00)00461-7]
 - 74 **Kirkpatrick AW**, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A,

- Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olivera C. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190-1206 [PMID: 23673399 DOI: 10.1007/s00134-013-2906-z]
- 75 **Prowle JR**, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010; **6**: 107-115 [PMID: 20027192 DOI: 10.1038/nrneph.2009.213]
- 76 **Haskins SC**, Hopper K, Rezende ML. The acid-base impact of free water removal from, and addition to, plasma. *J Lab Clin Med* 2006; **147**: 114-120 [PMID: 16503240 DOI: 10.1016/j.lab.2005.04.011]
- 77 **Gattinoni L**, Carlesso E, Maiocchi G, Polli F, Cadringer P. Dilutional acidosis: where do the protons come from? *Intensive Care Med* 2009; **35**: 2033-2043 [PMID: 19763537 DOI: 10.1007/s00134-009-1653-7]
- 78 **Carlesso E**, Maiocchi G, Tallarini F, Polli F, Valenza F, Cadringer P, Gattinoni L. The rule regulating pH changes during crystalloid infusion. *Intensive Care Med* 2011; **37**: 461-468 [PMID: 21152898 DOI: 10.1007/s00134-010-2095-y]
- 79 **Boyd JH**, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; **39**: 259-265 [PMID: 20975548 DOI: 10.1097/CCM.0b013e3181feb15]
- 80 **de Almeida JP**, Palomba H, Galas FR, Fukushima JT, Duarte FA, Nagaoka D, Torres V, Yu L, Vincent JL, Auler JO, Hajjar LA. Positive fluid balance is associated with reduced survival in critically ill patients with cancer. *Acta Anaesthesiol Scand* 2012; **56**: 712-717 [PMID: 22621427 DOI: 10.1111/j.1399-6576.2012.02717.x]
- 81 **Walsh SR**, Walsh CJ. Intravenous fluid-associated morbidity in postoperative patients. *Ann R Coll Surg Engl* 2005; **87**: 126-130 [PMID: 15826425 DOI: 10.1308/147870805X28127]
- 82 **Upadya A**, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA. Fluid balance and weaning outcomes. *Intensive Care Med* 2005; **31**: 1643-1647 [PMID: 16193330 DOI: 10.1007/s00134-005-2801-3]
- 83 **Lee J**, de Louw E, Niemi M, Nelson R, Mark RG, Celi LA, Mukamal KJ, Danziger J. Association between fluid balance and survival in critically ill patients. *J Intern Med* 2014; **277**: 468-477 [PMID: 24931482 DOI: 10.1111/joim.12274]
- 84 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubinfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580-637 [PMID: 23353941 DOI: 10.1097/CCM.0b013e31827e83af]
- 85 **Murphy CV**, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, Micek ST, Kollef MH. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; **136**: 102-109 [PMID: 19318675 DOI: 10.1378/chest.08-2706]
- 86 **Sakr Y**, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, Artigas A, Ranieri VM; Sepsis Occurrence in Acutely Ill Patients Investigators. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005; **128**: 3098-3108 [PMID: 16304249 DOI: 10.1378/chest.128.5.3098]
- 87 **Epstein CD**, Peerless JR. Weaning readiness and fluid balance in older critically ill surgical patients. *Am J Crit Care* 2006; **15**: 54-64 [PMID: 16391315]
- 88 **Payen D**, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; **12**: R74 [PMID: 18533029 DOI: 10.1186/cc6916]
- 89 **RENAL Replacement Therapy Study Investigators**; Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, Lo S, McArthur C, McGuinness S, Norton R, Myburgh J, Scheinkestel C, Su S. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. *Crit Care Med* 2012; **40**: 1753-1760 [PMID: 22610181 DOI: 10.1097/CCM.0b013e318246b9c6]
- 90 **Dulhunty JM**, Lipman J, Finfer S; Sepsis Study Investigators for the ANZICS Clinical Trials Group. Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. *Intensive Care Med* 2008; **34**: 1654-1661 [PMID: 18504549 DOI: 10.1007/s00134-008-1160-2]
- 91 **Bagshaw SM**, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care* 2008; **12**: 169 [PMID: 18671831 DOI: 10.1186/cc6948]
- 92 **Brower RG**, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; **351**: 327-336 [PMID: 15269312 DOI: 10.1056/NEJMoa032193]
- 93 **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.** *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
- 94 **Mekontso Dessap A**, Roche-Campo F, Kouatchet A, Tomicic V, Beduneau G, Sonnevillier B, Cabello B, Jaber S, Azoulay E, Castanares-Zapatero D, Devaquet J, Lellouche F, Katsahian S, Brochard L. Natriuretic peptide-driven fluid management during ventilator weaning: a randomized controlled trial. *Am J Respir Crit Care Med* 2012; **186**: 1256-1263 [PMID: 22997204 DOI: 10.1164/rccm.201205-0939OC]
- 95 **Van Biesen W**, Yegenaga I, Vanholder R, Verbeke F, Hoste E, Colardyn F, Lameire N. Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: a prospective analysis. *J Nephrol* 2005; **18**: 54-60 [PMID: 15772923]
- 96 **Bouchard J**, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76**: 422-427 [PMID: 19436332 DOI: 10.1038/ki.2009.159]
- 97 **Macedo E**, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease Study. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010; **14**: R82 [PMID: 20459609 DOI: 10.1186/cc9004]
- 98 **McDermid RC**, Raghunathan K, Romanovsky A, Shaw AD, Bagshaw SM. Controversies in fluid therapy: Type, dose and toxicity. *World J Crit Care Med* 2014; **3**: 24-33 [PMID: 24834399 DOI: 10.5492/wjccm.v3.i1.24]
- 99 **Peake SL**, Bailey M, Bellomo R, Cameron PA, Cross A, Delaney A, Finfer S, Higgins A, Jones DA, Myburgh JA, Sykes GA, Webb SA, Williams P. Australasian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study. *Resuscitation* 2009; **80**: 811-818 [PMID: 19467755 DOI: 10.1016/j.resuscitation.2009.03.008]
- 100 **Marik PE**. Early management of severe sepsis: concepts and controversies. *Chest* 2014; **145**: 1407-1418 [PMID: 24889440 DOI: 10.1378/chest.13-2104]
- 101 **Uchino S**, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacado E, Gibney N, Tolwani A, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; **32**: 1669-1677 [PMID: 15286542 DOI: 10.1097/01.CCM.0000132892.51063.2F]
- 102 **Prowle JR**, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. *Nat Rev Nephrol* 2014; **10**: 37-47 [PMID: 24217464 DOI: 10.1038/nrneph.2013.232]
- 103 **Ostermann M**, Alvarez G, Sharpe MD, Martin CM. Frusemide administration in critically ill patients by continuous compared to

- bolus therapy. *Nephron Clin Pract* 2007; **107**: c70-c76 [PMID: 17890871 DOI: 10.1159/000108641]
- 104 **Felker GM**, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; **364**: 797-805 [PMID: 21366472 DOI: 10.1056/NEJMoa1005419]
 - 105 **Caironi P**, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; **370**: 1412-1421 [PMID: 24635772 DOI: 10.1056/NEJMoa1305727]
 - 106 **Finfer S**, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247-2256 [PMID: 15163774 DOI: 10.1056/NEJMoa040232]
 - 107 **Martin GS**, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; **33**: 1681-1687 [PMID: 16096441 DOI: 10.1097/01.CCM.0000171539.47006.02]
 - 108 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31 [PMID: 17331245 DOI: 10.1186/cc5713]
 - 109 **Marik PE**, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 2013; **41**: 1774-1781 [PMID: 23774337 DOI: 10.1097/CCM.0b013e31828a25fd]
 - 110 **Schneider AG**, Baldwin I, Freitag E, Glassford N, Bellomo R. Estimation of fluid status changes in critically ill patients: fluid balance chart or electronic bed weight? *J Crit Care* 2012; **27**: 745.e7-745.12 [PMID: 22341728 DOI: 10.1016/j.jcrc.2011.12.017]

P- Reviewer: Markic D, Su M, Shou ZF, Trkulja V
S- Editor: Song XX **L- Editor:** A **E- Editor:** Lu YJ



Tumor lysis syndrome: A clinical review

Aibek E Mirrakhimov, Prkruthi Voore, Maliha Khan, Alaa M Ali

Aibek E Mirrakhimov, Prkruthi Voore, Maliha Khan, Alaa M Ali, Department of Internal Medicine, Saint Joseph Hospital, Chicago, IL 60657, United States

Author contributions: All the authors equally contributed to this work.

Conflict-of-interest: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Aibek E Mirrakhimov, MD, Department of Internal Medicine, Saint Joseph Hospital, 2900 N. Lake Shore, Chicago, IL 60657, United States. amirrakhimov1@gmail.com
Telephone: +1-773-6653015

Fax: +1-773-6653384

Received: October 10, 2014

Peer-review started: October 10, 2014

First decision: November 27, 2014

Revised: December 20, 2014

Accepted: February 10, 2015

Article in press: February 12, 2015

Published online: May 4, 2015

use of uric acid lowering agents and dialysis in refractory cases.

Key words: Cancer; Arrhythmia; Seizure disorder; Tumor lysis syndrome; Acute kidney injury

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Tumor lysis syndrome (TLS) is characterized by a massive tumor cell death leading to the development of metabolic derangements and target organ dysfunction. TLS can occur as a result of cancer treatment or spontaneously. Blood cancers constitute the vast majority of TLS cases because of the sensitivity to therapy and rapid division rates. Solid cancers comprise the minority of cases and are usually advanced if complicated by TLS. Prophylaxis is the mainstay of management and should be routinely implemented in high and intermediate risk patients. Management of established TLS includes intravenous hydration, urate lowering therapies, management of hyperkalemia and hemodialysis in refractory cases.

Mirrakhimov AE, Voore P, Khan M, Ali AM. Tumor lysis syndrome: A clinical review. *World J Crit Care Med* 2015; 4(2): 130-138 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i2/130.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i2.130>

Abstract

Tumor lysis syndrome is an oncometabolic emergency resulting from rapid cell death. Tumor lysis syndrome can occur as a consequence of tumor targeted therapy or spontaneously. Clinicians should stratify every hospitalized cancer patient and especially those receiving chemotherapy for the risk of tumor lysis syndrome. Several aspects of prevention include adequate hydration, use of uric acid lowering therapies, use of phosphate binders and minimization of potassium intake. Patients at high risk for the development of tumor lysis syndrome should be monitored in the intensive care unit. Established tumor lysis syndrome should be treated in the intensive care unit by aggressive hydration, possible use of loop diuretics, possible use of phosphate binders,

INTRODUCTION

Cancer disorders constitute a diverse group of pathologies in which abnormal metabolism and life cycle lead to the profound derangement of a host's metabolism. These cancers differ in their cellular origin, pathogenesis, clinical presentation, and management. Furthermore, cancer has been found by the Centers for Disease Control and Prevention to be the second leading cause of death among United States residents in 2011^[1]. Thus, because of the high prevalence of malignant neoplasms,

Table 1 Cairo-Bishop definition of laboratory tumor lysis syndrome for adults

Variable	Value	Change from baseline value
Uric acid	≥ 8 mg/dL (476 mmol/L)	25% increase
Potassium	≥ 6.0 mEq/L (or 6 mmol/L)	25% increase
Phosphorus	≥ 4.5 mg/dL (1.45 mmol/L) for adults and ≥ 6.5 mg/dL (2.1 mmol/L) for children	25% increase
Calcium	≤ 7 mg/dL (1.75 mmol/L)	25% decrease

Adapted from Cairo *et al*^[2].**Table 2** Cairo-Bishop grading of clinical tumor lysis syndrome for adults

Variable	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade V
Creatinine	None	1.5 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 1.5-3.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 3.0-6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated. Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Life-threatening (e.g., arrhythmia associated with HF, hypotension, syncope, shock). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Death
Seizures	None	-	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

Adapted from Cairo *et al*^[2]. ADL: Activities of daily living; HF: Heart failure; ULN: Upper limits of normal.

it is essential that clinicians are aware of the major complications of cancer itself and its management. Furthermore, it is likely that physicians will manage a greater number of cancer patients in future in the future, due to the improved survival rates of patients with cancer, ageing and growing population.

Tumor lysis syndrome (TLS) is a major oncometabolic entity requiring emergent recognition and management. TLS comprises a clinicolaboratory derangement of cellular metabolism, which can lead to severe renal impairment, cardiac arrhythmias, seizures, and death^[2]. Cellular death mediated by treatment targeted at cancer (chemotherapy or another pharmacological antitumor intervention, embolization of tumor or radiation therapy) or spontaneous cellular death in rapidly dividing cancer cells (which is known as spontaneous TLS) leads to an efflux of cellular material rich in potassium, phosphorus, and uric acid into the bloodstream. However, serum calcium levels typically decrease in patients with TLS because of its binding to excess phosphorus. These key metabolic derangements mediate the acute impairment of renal function, cardiac arrhythmogenicity, central nervous system toxicity, and ultimately death.

The most widely used diagnostic criteria are those proposed by Cairo *et al*^[2] in 2004. Based on this classification, TLS can be defined as laboratory TLS,

when TLS is clinically silent and only detected through laboratory work up, and clinical TLS, when laboratory TLS is complicated by the clinical manifestations mentioned above. The diagnostic criteria proposed by Cairo *et al*^[2] are presented in Tables 1 and 2. It is necessary to note that laboratory TLS is defined as the presence of at least two or more biochemical variables within the 3 d before chemotherapy or 7 d after chemotherapy in the face of adequate hydration and use of uric acid lowering agent. Clinical TLS is defined as the presence of at least one clinical criterion that is not believed to be attributable to the chemotherapy agent^[2]. However, our group has recently mentioned that this definition is imperfect since radiation therapy may lead to TLS as well, and TLS can occur spontaneously in rapidly proliferating and bulky malignancies^[3,4].

This manuscript summarizes the current state knowledge on TLS for clinicians involved in the care of critically ill patients: first, we briefly discuss the relevant pathobiology of TLS; second, we review and discuss which patients with cancer should be deemed to be at high risk; third, we go through the clinical presentation and diagnosis of TLS, including making an appropriate differential diagnosis; fourth, the information on TLS prevention is discussed; and finally, the treatment options for full blown TLS are provided.

SEARCH STRATEGY

We searched PubMed/Medline, Scopus, Embase, and the Web of Science for articles focused on TLS from 1950 to June 2014. The search terms were: tumor lysis syndrome, tumor lysis syndrome and renal impairment, tumor lysis syndrome and cardiac arrhythmias, tumor lysis syndrome and cardiac toxicity, tumor lysis syndrome and central nervous disease, and tumor lysis syndrome and seizures, as well as combinations of these. The reference lists of the identified articles were further screened for potentially relevant articles that could have been overlooked by an electronic search. The search methodology was adapted from the scientific search guidelines published in 2011^[5].

PATHOPHYSIOLOGY OF TLS

The basic understanding of the pathogenesis of TLS lies in the fact that cells and cancer cells in particular are rich in potassium, phosphorus, and uric acid. As mentioned previously, TLS can be either spontaneous when cancer cells die without the preceding chemotherapy, embolization, or radiation therapy, or secondary to cancer targeted treatment. In either case, the release of the above mentioned intracellular substances mediates the pathobiology of TLS and its complications.

Hyperkalemia is one of the key laboratory manifestations of TLS. Increased serum concentrations of potassium can adversely affect the skeletal muscle and cardiac myocardium^[6,7]. Indeed, hyperkalemia can mediate severe skeletal muscle dysfunction and weakness and induce various electrocardiogram (ECG) abnormalities including peaked narrow T waves, prolongation of the PR interval, prolongation of the QRS interval, as well as sine wave morphology^[8]. Ultimately, the cardiac effects of excess potassium can lead to ventricular tachyarrhythmias and death.

Uric acid is a byproduct of the purine nucleotides adenine and guanine, which constitute the backbone of nucleic acids^[9]. Put simply, purines are metabolized initially to hypoxanthine and xanthine *via* enzyme xanthine oxidase to uric acid, which is a final byproduct in humans. However, some mammals have an additional enzyme called urate oxidase that converts uric acid to the much more water soluble allantoin, which is easily removed by renal system. Given a high cellular turnover in cancer for whatever reason, huge amounts of nucleic acids, purines, and eventually uric acid are released and formed. Uric acid can crystalize and obstruct the flow in the renal tubules, leading to acute kidney injury^[2-4,10]. However, there are other mechanisms for uric acid mediated kidney impairment such as endothelial dysfunction and local ischemia, proinflammatory and prooxidative states, and impairment of local renal repair mechanisms^[10,11]. It is important to note that calcium phosphate crystals facilitate the deposition of uric acid in renal tissue^[2].

It is relevant to mention that in the contemporary

era most individuals at risk of TLS (at least in developed countries) or with a full-blown TLS are treated with hypouricemic agents, which minimize the impact of uric acid on the occurrence of acute kidney injury. An increase in serum phosphorus from cellular death can mediate acute kidney injury *via* similar mechanisms. When in excess, phosphorus tends to bind to calcium, forming the so-called calcium phosphorus product or calcium phosphate^[2-4]. This product can be deposited in kidneys, mediating acute kidney injury, as well as in cardiac tissue, leading to arrhythmia. Furthermore, a secondary decrease in free calcium concentration (due to phosphorus binding) is manifested by indications of central nervous toxicity such as seizures and psychiatric complaints, prolongation of the QT interval on ECG, and muscle tetany^[12]. It is interesting to observe that patients with spontaneous TLS may have lower rates of hyperphosphatemia due to phosphate uptake into rapidly dividing tumor cells^[3,4]. An increase in lactate dehydrogenase (LDH) is typically seen in patients with TLS, probably because of anaerobic glucose metabolism. However, the elevation of LDH is not included in the laboratory definition of LDH and it is important to note that LDH is a very sensitive but quite nonspecific marker for TLS.

In conclusion, it is important to note that preexistent renal disease and the characteristics of certain patients increase the risk of full-blown clinical TLS. These factors will be discussed in more detail in the next section.

POPULATION AT RISK

When assessing the risk of TLS in a particular patient, it is essential to bear in mind both the general and tumor-related predictors of risk.

An older age is associated with a reduction in the glomerular filtration rate^[13]. It is likely that advanced age predisposes to TLS *via* a decrease in the renal reserve, and may complicate volume replacement therapy due to higher rates of cardiac dysfunction. However, it is important to keep in mind that the impact of age on the occurrence of TLS has not been specifically studied. Other general patient characteristics such as volume depletion should be assessed and corrected if present. Patients afflicted with cancer often have decreased oral intake due to the decrease in appetite and nausea. Furthermore, cancer patients often suffer from vomiting and diarrhea, which can significantly diminish their volume status. Another important aspect which we routinely assess in our patients is the use of medications capable of detrimentally affecting renal function such as non-steroidal anti-inflammatory drugs, inhibitors of the angiotensin converting enzyme, and angiotensin receptor blockers, especially in patients with decreased volume status^[4]. The medication list of every patient should be reviewed and medications with a nephrotoxic renal profile should be discontinued wherever possible. It is important to consider that baseline kidney disease is a well-established risk factor for TLS^[4,14]. In addition,

a baseline increase in serum uric acid, phosphorus, potassium, and LDH also portends a greater risk of TLS^[4]. Other general comorbid conditions such as cardiac disease, diabetes mellitus, and renal disease should be considered prior to hydration since patients with these medical problems might easily develop symptomatic volume overload.

Another aspect of the risk stratification which we use is the type and burden of malignancy. We agree with the clinical risk stratification proposed by Cairo *et al.*^[15] who stratified cancers into three risk groups: a high risk group, an intermediate risk group, and a low risk group. The high risk group of cancers include advanced Burkitt's lymphoma/leukemia or early stage disease with elevated baseline LDH, acute lymphocytic leukemia (ALL) with white blood cell (WBC) count ≥ 100000 or less if the baseline elevation of LDH is twice the upper limit of normal (ULN), acute myeloid leukemia (AML) with WBC count ≥ 100000 , diffuse large B-cell lymphoma with an elevated baseline LDH of twice ULN, and bulky disease. Intermediate risk malignancies include AML with a WBC between 25000 and 100000, ALL with WBC < 100000 and an LDH of less than twice ULN, early stage Burkitt lymphoma/leukemia with an LDH of less than twice ULN, and diffuse large B-cell lymphoma with a baseline increase in LDH of twice ULN but non-bulky disease. Low risk diseases include indolent lymphomas, chronic lymphocytic leukemia, chronic myeloid leukemia in the chronic phase, AML with WBC count < 25000 and an LDH elevated to less than twice ULN, multiple myeloma, and solid cancers. Therefore, during our risk stratification we paid extra attention to patients with Burkitt's lymphoma/leukemia, ALL, AML, and diffuse large B cell lymphoma. Furthermore, we have recently reported that TLS in patients with solid malignancies may be higher than previously thought, and certain cancers with a sensitivity to therapy may be at higher risk for TLS, such as small cell lung cancer^[4].

In summary, it is recommended that both general and cancer-related factors are included in the risk assessment of every patient. Certain patient factors such advanced age and the presence of preexistent renal and cardiac diseases warrant a closer follow up during preventive hydration.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation and symptomatology is directly linked to the biochemical derangements observed in this disorder. As discussed earlier, the biochemical evidence of TLS includes hypocalcemia, hyperkalemia, hyperphosphatemia, and hyperuricemia^[2]. Therefore, the presentation of these biochemical disorders is typically represented by a clinical constellation of symptoms. For example, patients with TLS who have hypocalcemia may present with such symptoms as

nausea, vomiting, muscular hyperactivation such as spasms and tetany, seizures, prolongation of QT interval on the ECG, cardiac dysrhythmias, and alterations of mental status^[12]. Hyperphosphatemia may actually be a key mediator of acute kidney impairment as well as cardiac rhythm disturbances. Patients with hyperkalemia, if symptomatic, present with generalized fatigue, ECG abnormalities^[8], and serious cardiac arrhythmias including cardiac arrest. Elevations of uric acid can lead to acute renal insult manifested as an increase in serum creatinine and decrease in urine output.

Therefore, it is essential to be highly suspicious if any of the above symptoms arise in patients with cancer, especially those with tumors in a high risk group. In rare instances (at least in developed countries), TLS may present prior to the diagnosis of cancer. Nevertheless, a clinician should differentiate TLS from other causes of acute kidney injury such as sepsis, obstructive renal disease, medication toxicities (including those of chemotherapeutic agents), use of contrast dye for imaging studies, and rhabdomyolysis, as well as other rarer conditions such as vasculitis and primary glomerulopathies in appropriate clinical scenarios^[16]. Thus, a thorough clinical history is of paramount importance when dealing with a cancer patient who has presented with an acute decline in kidney function. The minimum amount of testing should include urinalysis and urine microscopy, comprehensive metabolic panel, uric acid, LDH, complete blood count, and renal ultrasound. The Cairo-Bishop criteria for the diagnosis of laboratory and clinical TLS are presented in Tables 1 and 2, respectively.

In conclusion, the clinical presentation of TLS is based on the constellation of individual metabolic derangements in a particular patient.

PREVENTION

It is essential to remember that the prevention of disease is always more cost-effective than the treatment of an established disease. Therefore, it is important to address and target any underlying kidney disease and possible hypovolemia before the start of cancer targeted therapies. Patients' management should be focused on the basis of the type of cancer and certain biochemical parameters such as LDH, phosphorus, uric acid, and potassium and serum creatinine, as discussed above. Subjects at intermediate and high risk of TLS should be monitored in a hospital setting and possibly in an intensive care unit (especially individuals at high risk of TLS). Potassium and phosphorus should be eliminated from the diet and intravenous (IV) fluids.

Several features are the mainstay of treatment for the prevention of TLS in patients undergoing active therapy. First, all patients at intermediate and high risk should be actively hydrated with IV fluids. Coiffier *et al.*^[17] recommended patients should be hydrated to

maintain urine output of at least 2 mL/kg per hour to minimize the risk of acute kidney injury. The choice of the fluid varies and some recommend the use of dextrose in one quarter normal saline as the initial fluid of choice^[17]. However, normal saline or lactated Ringer's solution are alternative choices, especially if the patient has other conditions such as dehydration, hypovolemia, and hyponatremia (it is essential to remember that lactated Ringer contains potassium and normal saline is associated with hyperchloremic metabolic acidosis)^[17]. Also, it is prudent to limit the calcium and potassium content of the IV fluids in such patients. Nevertheless, it is essential to note that some patients with cancer have underlying cardiorenal disease, which puts them at high risk of fluid overload and pulmonary edema. Such patients should be followed in closely monitored settings and there should be a low threshold for initiating loop diuretics if signs of fluid overload appear (shortness of breath, crackles on physical examination, desaturation, etc.). Loop diuretics are preferably used in clinical practice because of their potent diuretic properties as well as their hypokalemic effect, which can be of benefit in patients at risk of TLS. However, to the best of our knowledge there are no published scientific studies assessing the role of diuretics in the treatment of TLS.

Second, individuals at intermediate risk of TLS should be started on allopurinol at least 24 to 48 h prior to chemotherapy or radiation therapy to reduce the risk of uric acid nephropathy^[17]. Patients who do not tolerate oral medication such as those with severe nausea, vomiting, or altered function of the gastrointestinal tract can be given allopurinol IV. The recommended dose of allopurinol is up to 800 mg a day orally or 100 mg per square meter, and up to 600 mg a day for IV formulation^[17]. Allopurinol works by blocking the xanthine oxidase enzyme. In rare instances, allopurinol can lead to hypersensitivity reactions manifested as skin rashes, liver transaminitis, and acute kidney injury in the form of acute interstitial nephritis^[18]. Another important aspect of allopurinol use is the fact that the dose should be reduced in the event of chronic kidney disease^[19]. In such patients (intermediate risk, underlying renal disease, and/or history of allopurinol intolerance) the use of febuxostat may be considered, which is a relatively new xanthine oxidase inhibitor. Febuxostat does not require dose modification in patients with renal disease and does not seem to have allergy cross-reactivity with allopurinol^[20]. However, febuxostat has not been specifically studied for the population at risk of TLS or in patients with established TLS. Therefore, lack of specific data on febuxostat in patients with TLS should be mentioned during the management plan discussion with the patient and significant others, whenever appropriate.

Nevertheless, despite the availability of allopurinol, there is a significant number of patients who still develop significant kidney damage due to uric acid toxicity. As discussed above, some mammals (but not humans)

possess urate oxidase or uricase enzyme, which is capable of converting xanthine into allantoin. This is an important step since allantoin is easily excreted substance. A medication mimicking urate oxidase named rasburicase was approved by Food and Drug Association in 2012 for use in subjects at risk of TLS^[21]. Coiffier *et al*^[22] enrolled 100 patients with aggressive non-Hodgkin lymphoma to investigate whether the use of rasburicase is a safe and effective method of preventing TLS in a high risk group. Indeed, this investigation showed that rasburicase led to the normalization of uric acid within four hours of its administration, and it was well tolerated. Rasburicase provides much better control of uric acid than allopurinol (87% compared to 66%, respectively) as demonstrated in a study by Cortes *et al*^[23]. However, on the development of clinical TLS, no change between rasburicase and allopurinol was demonstrated^[23]. Similarly, in a recent meta-analysis published by Lopez-Olivo *et al*^[24], rasburicase was found to be effective in reducing uric acid levels, but it is unclear whether it led to better outcomes for clinical TLS.

Rasburicase should be used in individuals who are at high risk of developing TLS and in patients whose baseline uric acid is higher than 7.5 mg/dL (446 mmol/L)^[17]. The dosage of rasburicase is based on the underlying risk of TLS. Thus, in patients at high risk the recommended dose is 0.2 mg/kg daily and in patients with intermediate risk and whose baseline uric acid level is ≤ 7.5 mg/dL the suggested dose of rasburicase is 0.15 mg/kg daily^[17]. However, it is essential to mention that several small studies, most of which are retrospective in nature, have demonstrated that a single dose of rasburicase was effective^[25-27]. The dose of the rasburicase administered varies, but 6 mg of rasburicase has been shown to be effective^[27] and has provided uric acid control for 48 h after administration^[26]. Given the high cost of rasburicase, this may decrease the cost of treatment. This approach should be reserved for subjects at intermediate risk of TLS and allopurinol should usually be started simultaneously with rasburicase, unless contraindicated. Purine metabolism and the sites of action of allopurinol, febuxostat, and rasburicase are presented in Figure 1.

Despite being a safe agent, rasburicase should not be used in pregnant or lactating patients due to limited data on safety (pregnancy category C drug) and excretion into breast milk. Furthermore, it should not be used on patients with glucose 6 phosphate dehydrogenase deficiency due to the high risk of hemolysis and methemoglobinemia^[24,28].

Urine alkalization is another way of managing patients at risk of TLS. The rationale for this approach lies in the fact that an alkaline urine pH promotes uric acid solubility and its removal^[29]. Typically, a carbonic anhydrase inhibitor acetazolamide or sodium bicarbonate are used to reach a urine pH of at least 6.5. However, this approach has not been shown to be superior to the administration of normal saline alone^[29]. Furthermore, as

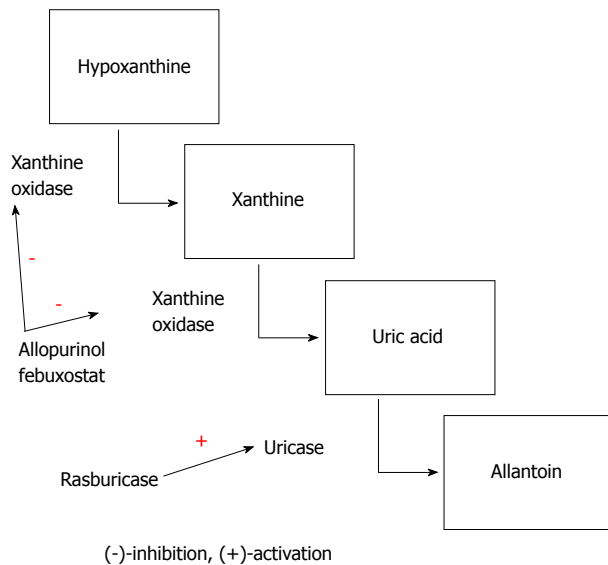


Figure 1 Purine metabolism and sites of action of allopurinol, febuxostat and rasburicase.

mentioned above, in the current era of the widespread use of uric acid lowering agents for TLS prevention, the role of calcium phosphate toxicity increases as a mediator of kidney damage in patients with TLS. In contrast to uric acid crystal deposition in acidic pH, the crystals of calcium phosphate more readily precipitate in alkaline pH, making this approach to alkalization potentially dangerous^[30]. Also, an alkaline pH promotes calcium binding to albumin, which can be very dangerous in patients with TLS who tend to have lower calcium levels at baseline, leading to neuromuscular and cardiac toxicity. Therefore, the current role of urine alkalization is of limited value and not recommended for routine use in patients at risk of TLS. It is also important to note that the use of phosphate binders in the prevention of TLS was not specifically studied in the literature. The decision to start phosphate binders should be decided on a case by case basis and always discussed with the patient prior to its initiation. The interested reader is referred to a recently published review on phosphate binders^[31].

Certain parameters should be monitored in individuals at high risk for TLS such as uric acid, phosphorus, potassium, and LDH 4 h after the initiation of chemotherapy or radiation therapy. The discontinuation of prophylaxis should be considered after the completion of cancer-related treatment when serum markers (uric acid, potassium, phosphorus, calcium, LDH, and creatinine) are within normal limits for at least two consecutive measurements several hours apart. It is reasonable to monitor patients for at least 24 h after discontinuation of TLS prophylaxis to ensure no development of TLS.

PRINCIPLES OF MANAGEMENT OF ESTABLISHED TLS

The treatment of fully blown TLS is based on the same

principles as its prevention. Patients with laboratory TLS and cardiorenal comorbid conditions, as well as patients with clinical TLS, should be admitted to an intensive care unit (ICU). Patients with TLS, unless anuric, should receive aggressive IV fluids with the goal of a urine output of at least 2 mL/kg per hour, as described above. Individuals deemed to be at increased risk of fluid overload, such as patients with cardiac and baseline renal disease, we consider the administration of IV loop diuretics such as furosemide to decrease the risk of pulmonary edema and augment urine output. Administration of loop diuretics may also improve control of hyperkalemia in patients with TLS. However, the role of loop diuretics is not based on solid data; thus, it should be approached on an individual basis.

As described above, the clinical spectrum of TLS includes laboratory abnormalities such as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia, which present clinically as cardiac arrhythmias, tetany, seizures, and acute kidney injury. We will briefly discuss the management of each laboratory abnormality one at a time. Hyperkalemia is a dangerous abnormality which may lead to muscle fatigue and cardiac toxicity and arrest^[8,32]. The reader is referred to a detailed review on the management of hyperkalemia^[32]. However, the management of hyperkalemia should always start from a 12-lead ECG. As discussed above, hyperkalemia may present with peaked narrow-based T waves, prolongation of the PR interval, loss of P waves, prolongation of the QRS interval, and the appearance of so called sine waves^[8]. Certain therapies are available for the management of hyperkalemia such as IV calcium products, IV insulin +/- dextrose, inhalational beta 2 agonists, IV sodium bicarbonate, cation exchange resins, and hemodialysis^[32]. Calcium in the form of gluconate or chloride should be administered IV (a typical dose is either 1 g of calcium gluconate and 500 mg to 1 g of calcium chloride) with certain ECG changes such loss of P waves and prolongation of the QRS interval^[32]. It is important to note that calcium chloride contains more calcium than calcium gluconate and should preferably be administered *via* a central line. IV calcium works by blocking the potassium effect on the cardiac cell membrane. However, it is essential to mention that in subjects with TLS calcium should be administered cautiously and ideally only in patients with severe ECG changes, malignant cardiac dysrhythmias, and cardiac arrest, and also in patients with severe neurological dysfunction such as seizures due to the possibility of forming a calcium phosphate product, which may lead to acute kidney injury^[33]. Furthermore, calcium products do not lower potassium levels and they must be used in conjunction with modalities which lower the serum concentration of potassium.

Albuterol, the most commonly used beta 2 agonist, which works by driving potassium into the cells, should be administered by a dose of 10 mg to 20 mg diluted in 4 mL of normal saline and nebulized during 10

min with a peak effect 90 min after administration^[32]. Generally, albuterol should be combined with IV insulin, with or without dextrose. Usually, 10 units of regular insulin should be administered, and if the serum glucose is < 250 mg/dL 50 mL of 50% dextrose should be administered^[32]. If the serum glucose is > 250, the administration of 50% dextrose is not necessary. IV insulin drives potassium into the cells in a similar way to albuterol and starts working 10 min after administration, peaks in 1 h, and lasts up to 6 h^[32]. A drop of potassium should be expected of up to 1.5 mmol/L after administration of both insulin and albuterol combined^[32]. The third option for reducing potassium is the administration of IV sodium bicarbonate in a dose of 50 mEq, which works by pushing potassium into the cells in exchange for hydrogen ions^[32]. However, it is necessary to remember that IV sodium bicarbonate is a weak agent with the best possible effect observed in patients with hyperkalemia and metabolic acidosis^[32]. Sodium bicarbonate should not be used as a sole agent in reducing elevated potassium. Furthermore, there are at least two factors that should be considered when using sodium bicarbonate in patients with TLS: first, alkalization may further decrease the free calcium concentration due to the greater binding of calcium to albumin, which might further decrease the physiologically active calcium; and second, urine alkalization might facilitate the deposition of calcium phosphate crystals in the kidney. Therefore, the general use of sodium bicarbonate in patients with hyperkalemia in the TLS setting is not recommended.

Another option for reducing potassium is the use of cation exchange resins such as sodium polystyrene sulfonate^[32]. Sodium polystyrene sulfonate works in the intestinal tract by binding potassium and exchanging it with sodium^[32]. The clinical effect of cation exchange resins typically starts within 2 h of administration and lasts up to 6 to 8 h. Sodium polystyrene sulfonate can be administered orally or as enema. The oral dose ranges from 15 to 45 g and can be repeated every 6 h as needed, while the enema is administered as 50 g of sodium polystyrene sulfonate mixed with water as a tap water enema. It is essential to note that sodium polystyrene sulfonate should not be used in patients with intestinal ileus or obstruction, and in post-operative patients due to higher risk of intestinal ischemia and necrosis^[32]. Also, whenever possible, patients with TLS should receive aggressive IV hydration (as with patients without end-stage renal disease who produce urine), and if needed with loop diuretics to minimize the chances of fluid overload as this will also promote the normalization of serum potassium. However, patients with refractory hyperkalemia should be strongly considered for renal replacement therapy, typically hemodialysis. In emergent cases where there is no permanent dialysis access, a short term dialysis catheter should be inserted.

One aspect of the management of elevated phosphorus in patients with TLS includes the restriction in phosphorus intake, both in diet and IV fluids. It is

necessary to mention that phosphate binders may be used in patients with hyperphosphatemia in the TLS setting. Phosphate binders include calcium containing medications such as calcium acetate and calcium carbonate, as well as non-calcium phosphate binders such as sevelamer and lanthanum^[31]. Phosphate binders should be taken with each meal and work by reducing the intestinal absorption of phosphorus^[31]. Calcium containing phosphate binders should theoretically be the first choice given the frequent presence of hypocalcemia in patients with TLS. However, there are no published scientific studies investigating the role of phosphate binders in the TLS setting. Hemodialysis or renal replacement therapy should be considered in patients with refractory hyperphosphatemia, in patients with symptomatic hypocalcemia, and with an elevated calcium phosphorus product of at least 70 mg²/dL². The calcium phosphorus product is calculated simply by multiplying the serum calcium and the phosphorus concentration. As discussed above, patients with TLS who have hypocalcemia should not be generally treated with calcium supplementation, given the higher risk of calcium phosphate crystallization and organ injury. However, calcium should be administered in the case of malignant cardiac arrhythmia (such as ventricular tachycardia or fibrillation), cardiac arrest, and seizure disorder. In the cardiac arrest setting, it is important to follow the advanced cardiac life support (ACLS) guidelines for its management and to exclude other possible causes of cardiac arrest such as hyperkalemia (common in TLS), hypokalemia, hypovolemia, acidosis (common in TLS, and which may be an indication for renal replacement therapy), hypothermia, tension pneumothorax, cardiac tamponade, thrombosis of the coronary and/or pulmonary circulation, as well as toxin exposure^[34]. In the same way, the approach to seizure in the TLS setting should include exclusion of hypoglycemia (and corrected if present), other metabolic abnormalities (hypo- or hypernatremia, hypomagnesemia), brain vascular abnormalities (hemorrhagic and ischemic strokes, subarachnoid hemorrhage, etc.), brain tumors or metastatic disease, toxin exposure (such as amphetamines, cocaine, tricyclic antidepressants, etc.), alcohol withdrawal, benzodiazepine withdrawal, brain infection, and others^[35].

Briefly, elevated levels of uric acid should be treated with rasburicase, unless contraindicated, in doses of at least 0.2 mg/kg once or twice a day. Allopurinol should only be considered if rasburicase is contraindicated or unavailable. Furthermore, it is essential to remember that allopurinol may actually increase the risk of acute kidney injury, given the increased production of xanthine, which is a poorly soluble bypass uric acid metabolite, as discussed above. In such patients early consideration of renal replacement therapy is advisable.

In conclusion, hemodialysis or other forms of renal replacement therapy should be considered in patients who are anuric, who have refractory hyperkalemia, symptomatic hypocalcemia, and with a calcium pho-

sphorus product of at least 70.

CONCLUSION

TLS is an oncometabolic emergency resulting from rapid cell death. TLS can occur as a consequence of tumor targeted therapy (chemotherapy, embolization therapy, and radiation therapy) or spontaneously. Clinicians should stratify every hospitalized cancer patient, especially those receiving chemotherapy, for the risk of TLS. Some aspects of prevention include adequate hydration, use of uric acid lowering therapies, use of phosphate binders, and the minimization of potassium intake. Patients at high risk for the development of TLS should be monitored in the ICU.

Treatment of established TLS should be taken in the ICU and includes aggressive hydration, the possible use of loop diuretics (especially for the patients prone to fluid overload), use of phosphate binders, use of uric acid lowering agents (preferably rasburicase), and dialysis in refractory cases.

REFERENCES

- Child Trends DATA BANK. Life expectancy. Available from: URL: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf
- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; **127**: 3-11 [PMID: 15384972 DOI: 10.1111/j.1365-2141.2004.05094.x]
- Ali AM, Barbaryan A, Zdunek T, Khan M, Voore P, Mirrakhimov AE. Spontaneous tumor lysis syndrome in a patient with cholangiocarcinoma. *J Gastrointest Oncol* 2014; **5**: E46-E49 [PMID: 24772347 DOI: 10.3978/j.issn.2078-6891.2014.012]
- Mirrakhimov AE, Ali AM, Khan M, Barbaryan A. Tumor Lysis Syndrome in Solid Tumors: An up to Date Review of the Literature. *Rare Tumors* 2014; **6**: 5389 [PMID: 25002953 DOI: 10.4081/rt.2014.5389]
- Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011; **31**: 1409-1417 [PMID: 21800117 DOI: 10.1007/s00296-011-1999-3]
- Espay AJ. Neurologic complications of electrolyte disturbances and acid-base balance. *Handb Clin Neurol* 2014; **119**: 365-382 [PMID: 24365306 DOI: 10.1016/B978-0-7020-4086-3.00023-0]
- McCullough PA, Beaver TM, Bennett-Guerrero E, Emmett M, Fonarow GC, Goyal A, Herzog CA, Kosiborod M, Palmer BF. Acute and chronic cardiovascular effects of hyperkalemia: new insights into prevention and clinical management. *Rev Cardiovasc Med* 2014; **15**: 11-23 [PMID: 24762462]
- Wagner GS, Strauss DG. Marriott's Practical Electrocardiography. 12th ed. New York, NY: LWW, 2013
- Álvarez-Lario B, Macarrón-Vicente J. Uric acid and evolution. *Rheumatology* (Oxford) 2010; **49**: 2010-2015 [PMID: 20627967 DOI: 10.1093/rheumatology/keq204]
- Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric Acid - key ingredient in the recipe for cardiorenal metabolic syndrome. *Cardiorenal Med* 2013; **3**: 208-220 [PMID: 24454316 DOI: 10.1159/000355405]
- Han HJ, Lim MJ, Lee YJ, Lee JH, Yang IS, Taub M. Uric acid inhibits renal proximal tubule cell proliferation via at least two signaling pathways involving PKC, MAPK, cPLA2, and NF-kappaB. *Am J Physiol Renal Physiol* 2007; **292**: F373-F381 [PMID: 16985215 DOI: 10.1152/ajprenal.00104.2006]
- Tohme JF, Bilezikian JP. Hypocalcemic emergencies. *Endocrinol Metab Clin North Am* 1993; **22**: 363-375 [PMID: 8325292]
- Esposito C, Plati A, Mazzullo T, Fasoli G, De Mauri A, Grosjean F, Mangione F, Castoldi F, Serpieri N, Cornacchia F, Dal Canton A. Renal function and functional reserve in healthy elderly individuals. *J Nephrol* 2007; **20**: 617-625 [PMID: 17918149]
- Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, Ortí G, Algarra L, Martínez J, Moscardó F, de la Rubia J, Jarque I, Sanz G, Sanz MA. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. *Haematologica* 2008; **93**: 67-74 [PMID: 18166787 DOI: 10.3324/haematol.11575]
- Cairo MS, Coiffier B, Reiter A, Younes A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol* 2010; **149**: 578-586 [PMID: 20331465 DOI: 10.1111/j.1365-2141.2010.08143.x]
- Lam AQ, Humphreys BD. Onco-nephrology: AKI in the cancer patient. *Clin J Am Soc Nephrol* 2012; **7**: 1692-1700 [PMID: 22879433 DOI: 10.2215/CJN.03140312]
- Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; **26**: 2767-2778 [PMID: 18509186 DOI: 10.1200/JCO.2007.15.0177]
- Keenan RT. Safety of urate-lowering therapies: managing the risks to gain the benefits. *Rheum Dis Clin North Am* 2012; **38**: 663-680 [PMID: 23137576 DOI: 10.1016/j.rdc.2012.08.008]
- Thurston MM, Phillips BB, Bourg CA. Safety and efficacy of allopurinol in chronic kidney disease. *Ann Pharmacother* 2013; **47**: 1507-1516 [PMID: 24259601 DOI: 10.1177/1060028013504740]
- Uloric® Product Monograph. Febuxostat Tablets, 80 mg. Xanthine Oxidase Inhibitor. Oakville, Ontario, Canada: Takeda Canada Inc., 2013
- Department of health and human services, Food and Drug Administration. Rasburicase Product Approval Information - Licensing Action 7/12/02. Malvern, PA: Sanofi-Synthelabo, Inc., 2012
- Coiffier B, Mounier N, Bologna S, Fermé C, Tilly H, Sonet A, Christian B, Casasnovas O, Jourdan E, Belhadj K, Herbrecht R. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; **21**: 4402-4406 [PMID: 14581437 DOI: 10.1200/JCO.2003.04.115]
- Cortes J, Moore JO, Maziarz RT, Wetzler M, Craig M, Matous J, Luger S, Dey BR, Schiller GJ, Pham D, Abboud CN, Krishnamurthy M, Brown A, Laadem A, Seiter K. Control of plasma uric acid in adults at risk for tumor Lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone--results of a multicenter phase III study. *J Clin Oncol* 2010; **28**: 4207-4213 [PMID: 20713865 DOI: 10.1200/JCO.2009.26.8896]
- Lopez-Olivo MA, Pratt G, Palla SL, Salahudeen A. Rasburicase in tumor lysis syndrome of the adult: a systematic review and meta-analysis. *Am J Kidney Dis* 2013; **62**: 481-492 [PMID: 23684124 DOI: 10.1053/j.ajkd.2013.02.378]
- Reeves DJ, Bestul DJ. Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. *Pharmacotherapy* 2008; **28**: 685-690 [PMID: 18503395 DOI: 10.1592/phco.28.6.685]
- Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. *J Clin Pharm Ther* 2009; **34**: 207-213 [PMID: 19250141 DOI: 10.1111/j.1365-2710.2008.00994.x]
- McBride A, Lathon SC, Boehmer L, Augustin KM, Butler SK, Westervelt P. Comparative evaluation of single fixed dosing and weight-based dosing of rasburicase for tumor lysis syndrome. *Pharmacotherapy* 2013; **33**: 295-303 [PMID: 23456733 DOI: 10.1002/phar.1198]
- Sonbol MB, Yadav H, Vaidya R, Rana V, Witzig TE. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol* 2013; **88**: 152-154 [PMID: 22573495 DOI: 10.1002/ajh.23182]
- Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis

- and prevention of acute urate nephropathy. *J Clin Invest* 1977; **59**: 786-793 [PMID: 16037 DOI: 10.1172/JCI108700]
- 30 **Worcester EM**, Coe FL. Clinical practice. Calcium kidney stones. *N Engl J Med* 2010; **363**: 954-963 [PMID: 20818905 DOI: 10.1056/NEJMcp1001011]
 - 31 **Malberti F**. Hyperphosphataemia: treatment options. *Drugs* 2013; **73**: 673-688 [PMID: 23625273 DOI: 10.1007/s40265-013-0054-y]
 - 32 **Maxwell AP**, Linden K, O'Donnell S, Hamilton PK, McVeigh GE. Management of hyperkalaemia. *J R Coll Physicians Edinb* 2013; **43**: 246-251 [PMID: 24087806 DOI: 10.4997/JRCPE.2013.312]
 - 33 **Howard SC**, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med* 2011; **364**: 1844-1854 [PMID: 21561350 DOI: 10.1056/NEJMra0904569]
 - 34 **Neumar RW**, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, Kudenchuk PJ, Ornato JP, McNally B, Silvers SM, Passman RS, White RD, Hess EP, Tang W, Davis D, Sinz E, Morrison LJ. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; **122**: S729-S767 [PMID: 20956224 DOI: 10.1161/CIRCULATIONAHA.110.970988]
 - 35 **Angus-Leppan H**. First seizures in adults. *BMJ* 2014; **348**: g2470 [PMID: 24736280 DOI: 10.1136/bmj.g2470]

P- Reviewer: Lin J, Muensterer OHJ **S- Editor:** Tian YL

L- Editor: A **E- Editor:** Lu YJ



Designing drug regimens for special intensive care unit populations

Brian L Erstad

Brian L Erstad, Department of Pharmacy Practice and Science, University of Arizona College of Pharmacy, Tucson, AZ 85721-0207, United States

Author contributions: Erstad BL solely contributed to this work.

Conflict-of-interest: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Brian L Erstad, PhD, MCCM, Department of Pharmacy Practice and Science, University of Arizona College of Pharmacy, 1295 N. Martin Ave., Tucson, AZ 85721-0207, United States. blerstad@hotmail.com

Telephone: +1-520-6264289

Fax: +1-520-6267355

Received: August 5, 2014

Peer-review started: August 6, 2014

First decision: August 28, 2014

Revised: September 6, 2014

Accepted: February 4, 2015

Article in press: February 9, 2015

Published online: May 4, 2015

Abstract

This review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions. The data sources included a literature search of MEDLINE and EMBASE with reviews of reference lists of retrieved articles. Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe

forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy. Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients were extracted. Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses. Critically ill patients with changes in body size, habitus and composition require special consideration when designing medication regimens, but there is a paucity of literature on which to make drug-specific, high-level evidence-based recommendations. Based on the evidence that is available, general recommendations are provided for drug choice or dosing in special critically ill populations.

Key words: Drug dosage calculations; Pharmacokinetics; Critical care; Body composition; Obesity; Pregnancy

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Special populations of intensive care units patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

Erstad BL. Designing drug regimens for special intensive care unit populations. *World J Crit Care Med* 2015; 4(2): 139-151 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i2/139.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i2.139>

INTRODUCTION

What are special populations?

The term "special populations" does not have a uniform definition. For example, within the National Institutes of Health (NIH) there is an Office for Special Populations within the National Institute of Mental Health (<http://www.nimh.nih.gov/about/organization/od/office-for-special-populations-osp.shtml>) that refers to "the mental health needs of women and minority populations". On the other hand, there is an Office of Special Populations within the National Institute on Aging (<http://www.nia.nih.gov/about/offices/office-special-populations>) refers to "older women, minorities, and persons with disabilities" and the National Institute on Alcohol Abuse and Alcoholism (<http://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders>) that refers to "Special populations are groups who face particular risks from drinking alcohol based on personal characteristics such as age or gender". The overarching theme to these definitions is that they try to focus on the special populations of particular importance to each institute. Along those lines, this review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions.

LITERATURE STUDY

Data sources

Searches of MEDLINE and EMBASE were performed. The search strategies were developed in cooperation with a medical librarian with training in the performance of systematic reviews. The initial search strategy for MEDLINE was: (((("critical care" (MeSH Major Topic) or "critically ill patients" or "critically ill" or "critical patients" or "critical patient") and (((("physiological phenomena" (MeSH Terms)) or "body composition" (MeSH Terms) or "body size descriptors" or "body weight changes" or "body weight change" or "body size" or "body composition" or "physical body change" or "body change")))) and English (lang)))). For EMBASE the initial search strategy was: "intensive care"/exp or "critical care": ab,ti or "critically ill patients": ab,ti or "critically ill":ab,ti or "critical ill":ab,ti or "critical patient":ab,ti and ("body weight"/exp or "weight change"/exp or "weight fluctuation"/exp or "weight, mass and size"/exp or "body composition"/exp or "body weight change":ab,ti or "body weight changes":ab,ti or "body size":ab,ti or "body composition":ab,ti or "physical body change":ab,ti) and (English)/lim and [(embase)/lim or (embase classic)/lim]. Subsequent searches were performed looking at more specific special populations. For example for MEDLINE: (((("critical care" (MeSH Terms) or "critically ill patients" or "critically ill" or "critical patients" or "critical patient") and ("body composition" (MeSH

Terms) or "body size descriptors" or "body weight changes" or "body weight change" or "body size" or "body composition" or "physical body change" or "body change" or "Overweight" (Mesh) or "Obesity" (Mesh) or "overweight" or "obese" or "obesity" or "Thinness" (Mesh) or "underweight" or "Amputation Stumps" (Mesh) or "short limbs" or "missing limbs" or "Pregnant Women" (Mesh) or "Pregnancy" (Mesh) or "pregnant patients" or "pregnant women" or "Extracorporeal Membrane Oxygenation" (Mesh) or "Plasma Exchange" (Mesh))) and ("Treatment Outcome" (Mesh) or "Pharmaceutical Preparations" (Mesh) or "medication regimen" or "medication regimens" or "Patient Care Planning" (Mesh) or "Patient Care Management"(Mesh) or "Therapeutics" (Mesh) or "Drug Therapy" (Mesh) or "Drug Delivery Systems" (Mesh))).

Study selection

Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation (ECMO) or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy.

Data extraction

Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients.

Data synthesis and analysis

Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses (Table 1). For this reason, it was decided to focus this review on general principles related to drug choice or dosing in special populations of critically ill patients, rather than trying to provide specific dosing recommendations for every medication that might be used in the intensive care units (ICU) setting^[1]. Selected medications will be discussed to provide examples of dosing issues, but most of the references will list review articles and guidelines of particular relevance to the special population under consideration. Recommendations that are provided are done so under the assumption that there are no concomitant therapies or co-morbidities that would alter the parameter of interest. It is also presumed that additional expertise, such as that of a clinical pharmacist, will be sought when dealing with these difficult therapeutic decisions.

This paper will be divided into 2 parts beginning in Part 1 with an overview of body composition and how various size descriptors such as body weight that are used for drug dosing reflect changes in body

Table 1 Results of search strategies for randomized controlled trials

	Number of citations
MEDLINE	
Initial search strategy as described in text	5316
Search strategy limited to "clinical trial" and "humans"	726
Of the 725 citations, the number of RCTs with clinically relevant endpoints	0
MEDLINE	
Focused search strategy as described in text	2586
Search strategy limited to "clinical trial" and "human"	176
Of the 176 citations, the number of RCTs with clinically relevant endpoints	0
EMBASE	
Initial search strategy as described in text	1898
limited to terms indexed as major focus	
Search strategy limited to "human" or "clinical trial"	1431
Search strategy limited to "article"	870
Of the 871 citations, the number of RCTs with clinically relevant endpoints	0

RCT: Randomized controlled trial.

composition. The remaining sections of Part 1 deal with pharmacokinetic and therapeutic drug monitoring considerations when selecting and dosing drugs in special populations. Part 2 of this paper will highlight specific populations with changes in body size, habitus and composition that require special consideration when designing drug regimens: obese patients, patients who are underweight, amputated or missing limbs, pregnant patients, and patients undergoing ECMO or plasma exchange.

PART 1

Body composition

Body size and shape (also known as habitus) refer to physical attributes of individuals such as height, weight, and body proportions. Anthropometry is the measure of such attributes. Epidemiological studies conducted in the United States have demonstrated not only an increase in attributes such as weight but also increased variability in anthropometric indicators with implications for drug dosing^[2]. Table 2 lists body composition changes that frequently occur in critically ill patients during more prolonged ICU stays.

There are a number of techniques for assessing body composition that have been used to assess tissue differences such as fat vs fat-free mass, but have yet to receive widespread use in the clinical arena^[3]. While much of this research has focused on the nutritional aspects of body composition measurements^[4], the metabolic aspects of the measurements have implications for the pharmacokinetics and pharmacodynamics of medications^[5]. Approximately 25% of weight gain or loss is fat free mass^[6]. Further, different types of adipose

Table 2 Changes in body composition during intensive care units stay that may affect drug disposition

Lean vs adipose tissue changes during more prolonged stay
 Loss of lean tissue
 Gain of adipose tissue
 Distribution of adipose tissue (e.g., subcutaneous vs visceral)
 Gains or losses of total body water throughout stay
 Distribution of retained fluid (e.g., intracellular vs extracellular, interstitial vs intravascular)

Reprinted with permission from Erstad^[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Table 3 Weight descriptors commonly used in adult patients in the clinical setting

Ideal body weight (IBW)
 IBW in kg for men = 50 kg + 2.3 kg for each inch in height over 60 inches
 IBW in kg for women = 45.5 kg + 2.3 kg for each inch in height over 60 inches
 Adjusted body weight (ABWadj)
 ABWadj in kg = IBW + 0.4 (actual weight - IBW)
 Lean body weight (LBW)
 LBW (men) = $(1.10 \times \text{weight in kg}) - \{120 \times [(\text{weight in kg}) / (\text{height in cm})]^2\}$
 LBW (women) = $(1.07 \times \text{weight in kg}) - \{148 \times [(\text{weight in kg}) / (\text{height in cm})]^2\}$
 Body mass index (BMI)
 BMI = actual body weight (ABW) in kg divided by (height in m)²
 Body surface area (BSA) in m²
 BSA = square root [(height in cm × ABW in kg) / 3600]

Various methods have been used for estimation - inclusion in this table should not be interpreted as support for a particular method. Reprinted with permission from Erstad^[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

tissue have differing metabolic activity. Brown adipose tissue has been investigated as an anti-obesity tissue^[7].

Size descriptors

Since sophisticated technologies for assessing body composition are not typically employed in the ICU setting, most prognostic and drug dosing information based on physical attributes is derived from basic size descriptor information such as height, weight, sex or some combination of these variables (see Table 3). In particular, body mass index has been studied as an indicator of morbidity and mortality in critically ill patients. The relationship between body mass index and mortality is not linear and there appears to be a so-called obesity paradox in which obese patients as defined by a BMI range between 30 and 39.9 kg/m² have a lower ICU mortality compared to patients of more extreme weights^[8,9].

While commonly used to categorize and stratify patients by height and weight, body mass index is used less frequently as a size descriptor for drug dosing. The choice of size descriptor for drug dosing is between actual body weight or some type of adjusted

Table 4 Estimates and measurements of size descriptors such as height and weight

Strive for consistency and standardization within and between all healthcare professionals and staff involved in size descriptor estimates and measurements. Examples include:
Method of estimates including formulas and equations used for calculations
Instruments used for measurement and how utilized (e.g., clothes off or on for weight recordings)
Recording and use of units of estimates and measurements (e.g., centimeters <i>vs</i> inches, pounds <i>vs</i> kilograms)
Terminology related to size descriptors (e.g., ideal weight, adjusted weight)
Ensure proper communication and documentation of method (e.g., patient <i>vs</i> provider, estimate <i>vs</i> measurement) used to obtain estimates and measurements of size descriptors
Have ongoing education with evaluation of all personnel involved in the determination and documentation of estimates and measurements
Have periodic evaluation of compliance by area (e.g., ICU <i>vs</i> emergency department)
Ensure that age-appropriate instruments are available and have regularly scheduled calibration
Use technology (e.g., automated infusion devices, dosing calculators) when available to reduce chance of medication errors

Reprinted with permission from Erstad^[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. ICU: Intensive care units.

Table 5 Pharmacokinetic considerations in the critically ill patient

Data from pharmacokinetic studies are no substitute for clinical monitoring of the individual patient's response to therapy
Pharmacokinetic parameters derived from studies involving normal volunteers or less severely ill patients are not directly applicable to the critically ill patient
Average parameters for volume of distribution and clearance are larger and have much greater variability in critically ill patients compared with less severely ill patients
The duration of action of single or isolated IV doses of more lipophilic drugs used in the ICU is a function more of distribution than of clearance
The values for volume of distribution and clearance frequently change from baseline with prolonged drug administration because of factors such as accumulation or altered elimination
For drugs with active metabolites, the pharmacokinetics of the metabolites as well as the parent compound must be considered
Drug absorption is important not only with oral or enteral administration but also with intramuscular and subcutaneous injections

Reprinted with permission from Erstad^[56]. ICU: Intensive care units.

body weight. Clearly, there are implications for body composition differences on medications dosed based by body weight even when weight is appropriately measured^[10]. Table 4 describes some of the more important issues to consider relative to size descriptor measurements.

Pharmacokinetic considerations and therapeutic drug monitoring

Volume of distribution is the pharmacokinetic parameter of most importance for giving loading doses of drugs and it is expected that more lipophilic drugs would have more extensive distribution. Lean body weight appears to be more predictive of renal clearance than actual body weight for obese patients, but there is substantial variation in clearance in critically ill patients^[11,12]. Further, critically ill patients may have augmented measured creatinine clearance values^[13].

An understanding of the concept of dose proportionality is important for deciding how to apply pharmacokinetic data from patients with near-normal body size and shape to patients with more extreme forms of size, shape and body composition. Basically, dose proportionality suggests that pharmacokinetic parameters change in the same direction and same degree as changes in body weight. Tables 5 and 6 describe important considerations when evaluating pharmacokinetic and dose proportionality issues in critically ill patients.

Because drug dosing based on pharmacokinetic parameters is often insufficient to accurately predict pharmacologic effects in individual patients, therapeutic drug monitoring may help to provide additional information about the body's handling of a drug. Unfortunately, in most clinical settings, only a limited number of drugs have assays for assessing concentrations of the drugs in the body; even when such assays are available, they do not always have a clear-cut correlation with the pharmacodynamic and pharmacological properties of a particular drug (Table 7). Importantly, this discussion of pharmacokinetics and therapeutic drug monitoring is based on generalizations and should not be used to guide dosing regimens of specific drugs. Instead, drug dosing regimens in patients of more extreme body compositions should be based on evidence from a variety of sources as exemplified by the approach used in Table 8 for obese patients.

PART 2

Drug dosing in obese patients

It is not surprising that epidemiological studies continue to track the prevalence and markers (e.g., body mass index) of obesity and associated health outcomes. What is surprising is the relative lack of data on drug dosing in obesity, particularly in patients with more extreme forms of obesity^[14]. Currently, there is no mandate that

Table 6 Assessment of possible dose proportionality in studies with obese subjects¹

Did the study involve a comparator group of normal weight subjects of similar demographics (e.g., age, height, gender) and co-morbidities as the obese subjects?
Did the values of pharmacokinetic parameters unadjusted for bodyweight (e.g., volume of distribution in mL and clearance in mL/min) increase proportionally to weight in the obese <i>vs</i> the normal-weight subjects?
Were the values of pharmacokinetic parameters adjusted for actual bodyweight (e.g., volume of distribution in mL/kg and clearance in mL/min per kilogram) similar in the obese and normal-weight subjects?
Did the values of pharmacokinetic parameters adjusted for ideal bodyweight (e.g., volume of distribution in mL/kg and clearance in mL/min per kilogram) increase proportionally to weight in the obese <i>vs</i> the normal-weight subjects?
Was the calculated half-life based on the pharmacokinetic parameters similar in the obese and normal-weight subjects?
When actual bodyweight was used in weight-based dosing protocols were the therapeutic effects and dose-related adverse drug events similar in the obese and normal-weight subjects?

¹If the answers to all of these questions are yes, the data suggests that dose proportionality is present, although this does not necessarily mean that actual bodyweight should be used in weight-based dosing protocols. Reprinted with permission from Erstad^[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Table 7 Considerations with therapeutic drug monitoring

Blood concentration measurements are not available for the majority of drugs used in critically ill patients
So-called therapeutic ranges for therapeutic drug monitoring (TDM) are typically derived from studies involving small numbers of patients
Most therapeutic ranges are based on steady-state drug concentrations, so non-steady-state concentrations can be very difficult to interpret (and often meaningless)
Disease states that affect a drug's volume of distribution or clearance often negate the presumption of steady-state conditions necessary for proper interpretation of concentrations
The minimum and maximum concentrations used to define a therapeutic range are often quite arbitrary and not necessarily applicable to a specific patient
The free or unbound form of a drug is the active form, but the total drug concentration is most commonly measured by clinical laboratories
Total drug concentrations for a drug with high protein binding (e.g., > 90%) can be difficult to interpret when protein concentrations are decreased or when other drugs or diseases displace drug
Clinical response, not a TDM measurement, should be the primary driver of dosing decisions
The administration and timing of drug doses prior to TDM measurement should be verified, not presumed, because these affect the proper interpretation of the measurement
TDM is most useful when clinical indicators are misleading or not available or when the clinical indicator is a problem that the clinician is trying to prevent (e.g., aminoglycoside nephrotoxicity)
Unnecessary TDM should be avoided (e.g., ordering daily measurements of drug concentrations for a drug with a long half-life) because it may lead to inappropriate changes and unnecessary TDM costs

Reprinted with permission from Erstad^[56].

product labeling provide information on drug dosing in obesity, or for that matter, what weight should be used for weight-based dosing of medications. Even the word "weight" as used in most product brochures is not defined, so an assumption is usually made by clinicians that the term is referring to actual body weight. For drugs that have non-weight-based dosing regimens (e.g., mg per dose rather than mg/kg per dose), the clinician make elect to use the higher end of the dosing range for drugs with a rather wide therapeutic index. The issue becomes more complicated for weight-based dosing regimens in which the choice of weight is not clear.

When dosing an obese patient on a drug that does not include specific recommendations in the product labeling, the first step should be to perform a literature search looking for relevant investigations. The clinician may find that key studies involving a drug included patients with more mild to moderate forms of obesity (BMI < 35), suggesting that weight-based dosing with the use of actual body weight is applicable. When such

studies with direct applicability to a particular patient are not available, the clinician will likely have to extrapolate from the evidence that does exist; often, this evidence is limited to pharmacokinetic investigations where an assessment of dose proportionality is needed. For the majority of drugs commonly used in the ICU setting, there is little evidence to suggest the use of actual body weight for weight-based dosing regimens in more severe forms of obesity^[15]. The recommendation for the use of actual body weight for maintenance dosing of vancomycin is a notable exception, not the rule, for most of these drugs. This is not totally unexpected given that many of these drugs are eliminated by the kidneys and the most accurate estimations of creatinine clearance in more extreme forms of obesity have been made using equations based on lean or another form of adjusted body weight^[16]. Similarly, loading doses of drugs that primarily distribute into the intravascular compartment would likely require dosing based on a lean or adjusted body weight for weight-based dosing regimens given that blood volume does not increase

Table 8 Conceptual framework for dosing medications in obese patients¹

<p>Step 1</p> <p>Evaluate the clinical investigations involving the medication to determine the degree of obesity in the patients under study and the weight descriptor used for dosing, which is usually actual body weight (ABW) in studies leading to medication approval. Determine if the patient under consideration appears to fit the profile of the patients in the study; be particularly cautious if the patient is extremely obese. If the patient appears to fit the profile of the patients in the studies, use the weight descriptor. If not, proceed to Step 2</p> <p>↓</p> <p>Step 2</p> <p>If the patient does not fit the profile of the patients in the clinical investigations, search the literature for pharmacokinetic studies involving the medication in obese patients. Assess whether the pharmacokinetic parameters of the medication appear to increase proportionately with increasing weight suggesting that use of ABW may be appropriate. If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 3</p> <p>↓</p> <p>Step 3</p> <p>If the patient does not fit the profile of the patients in the clinical investigations and if no pharmacokinetic studies involving the specific medication in obese patients are available, evaluate the literature for dosing studies in obese patients with medications that have similar physicochemical and pharmacokinetic parameters (<i>e.g.</i>, medications in the same class). If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 4</p> <p>↓</p> <p>Step 4</p> <p>If no relevant studies can be found, and particularly if the patient is extremely obese, assess whether an alternative medication (where more is known about dosing in obese patients) might be appropriate. If there is no equivalent or better medication option available, proceed to Step 5</p> <p>↓</p> <p>Step 5</p> <p>Assess the benefits and risks of using ABW for dosing using step 5a for weight-based dosing or 5b for non-weight based dosing</p> <p>Step 5a</p> <p>If weight-based dosing (<i>e.g.</i>, mg/kg) is being used, assess whether the potential benefits of using ABW (<i>e.g.</i>, need to reach therapeutic range quickly) are likely to exceed the potential risks of over-dosing. If the patient under consideration is substantially heavier than the patients in the investigations or if no studies are available, assess whether a lean body weight or adjusted body weight equation might be preferable, especially in medications with a narrow therapeutic range and small (<i>e.g.</i>, < 0.2 L/kg) to moderate (<i>e.g.</i>, 0.2 to 1 L/kg) volumes of distribution that are cleared primarily by glomerular filtration</p> <p>Step 5b</p> <p>If non-weight-based dosing (<i>e.g.</i>, mg/ dose) is being used, assess whether the potential benefits of using a larger dose are likely to exceed the potential risks of over-dosing if the patient under consideration is substantially heavier than the patients who were enrolled in the clinical investigations involving the medication, and if the medication has a narrow therapeutic range and a moderate (0.2 to 1 L/kg) to large (> 1 L/kg) volume of distribution</p>
--

¹Should always take into account potential co-morbidity confounders such as renal or liver dysfunction when determining dosing regimens. Reprinted with permission from Erstad^[57].

proportionally to increasing fat weight; importantly, the standard variation of both creatinine clearance and plasma volume measurements become larger in more severely obese patients^[17,18].

Recommendations

For patients with mild-moderate forms of obesity (BMI < 35), dosing recommendations provided in the product information and other reputable drug information sources are usually appropriate since the studies that led to drug approval likely included such patients. The issue of dosing is more complicated in patients with more extreme forms of obesity since such patients are often either excluded from studies or included in such small numbers that a sub-analysis of data is inadequately powered to provide meaningful conclusions. When dosing these patients in the ICU setting the clinician will likely need to extrapolate dosing information from other similar drugs (*e.g.*, drugs in the same structural class) when such information is available and from investigations evaluating the drug's physicochemical and pharmacokinetic properties. Finally, the benefit vs risk assessment of using actual body

weight for weight-based dosing of a drug should take into account the fact that most renally-eliminated drugs studied to date have not exhibited dose proportionality in patients with extreme forms of obesity; in other words, renal clearance of the drug does not increase proportionately with increasing body weight suggesting that an adjusted weight would be more appropriate to use when designing weight-based dosing regimens in severely obese patients.

Drug dosing in patients who are underweight, short, or have amputations or missing limbs

Based primarily on indirect evidence, underweight or short (assuming relatively normal body weight for height) patients are usually dosed on the lower end of dosing ranges for non-weight based dosing regimens. Such dosing is predicated on the assumption that the proportion of lean or metabolically active tissue is similar to that of patients of more normal weight and stature. However, an interesting issue arises when it is decided to use ideal body weight for a drug that has weight-based recommendations. The formulas most commonly used for dosing ideal body weight are based

on calculations that assume the patient is at least 5 feet tall. For example, for a male, one ideal body weight equation is calculated by adding 2.3 kg for each inch above 5 feet tall with a 50 kg base weight for the first 5 feet. While not based on any solid evidence, some clinicians have estimated the ideal body weight for a person less than 5 feet tall by subtracting 2.3 kg for each inch below 5 feet. Others have used regression analysis, typically on older data, to derive estimations for individuals less than 5 feet. With any of these methods, the estimates are likely to be less precise the shorter the patient. Similar issues would arise when estimating ideal body weight in patients who are missing body parts such as an arm or leg.

Recommendations

For non-weight-based dosing, usual or slightly lower than usual doses likely will suffice, assuming all other factors such as body weight and renal function are near normal. For weight-based dosing, there are a couple of options. Particularly for drugs with a wide therapeutic index, one could use actual body weight with the assumption that the missing limb had metabolic activity similar to the rest of the body. Also as above, the issue arises as to which weight to use when calculating an ideal body weight. One method that has been used in this situation for nutritional assessment is based on body part proportionality^[19]. With this method, different body segments are assigned a percentage of total body weight. For example, a leg with a foot might comprise 16% of the total body weight, so the ideal body weight calculation in a patient with a leg amputation would be lowered by 16%. For an obese patient with this same amputation, the ideal body weight would be calculated in the same manner. If this same obese patient was being dosed by some other adjusted body weight equation (e.g., ideal weight plus 40% of the excess weight), then the ideal body weight that takes into account the missing leg would be calculated first and used in the adjusted body weight equation. It is unknown if these methods of ideal body weight correction are more accurate or appropriate than an uncorrected (and easier to calculate) ideal body weight estimation for drug dosing.

None of these methods has been validated; further, the methods for calculating ideal body weight in patients of short stature do not take into account possible fat weight associated with obesity. If used, any of these dosing estimations should have some form of verification through therapeutic drug monitoring if available and/or through pharmacologic endpoints.

Drug choice or dosing in pregnancy

In general, pregnant or postpartum women account for a relatively small percent of ICU admissions, although the numbers are dependent on the type and location of hospital^[20]. Traumatic injuries occur in approximately 7% of pregnancies in the United

States^[21]. Apart from the direct adverse consequences of the trauma or underlying disease states in the pregnant woman, there are special considerations for drug dosing not only because of physiological changes in the mother, but also because of potential fetal risk. The current FDA labeling of drugs is based on risk categories A, B, C, D, and X, although this system is currently undergoing revision by the FDA because of confusion associated with risk/benefit interpretation. It is important to note that these categories do not represent a linear increase in risk, since categories C, D, and X each involve a risk/benefit assessment. Such an assessment should take into account the timing of drug administration is important; for example, the critical period for embryonic organ formation is during weeks 3 to 8 post-conception. It has been estimated that approximately 66% of all drugs are category C^[22]. In light of these categorical limitations, other references have been developed to provide the clinician with more information for drug use in pregnancy^[23]. However, the quality and usefulness of the data in such sources is a function of the method of data collection, which in the case of fetal adverse drug events in pregnancy is data from case reports and registries. Both the numerator (i.e., number of subjects with a reported adverse event) and the denominator (total number of subjects receiving the drug) are unlikely to be accurate with these collection techniques, so a true incidence is unknown, assuming causality does exist. Also largely unknown is how the duration of drug exposure relates to potential fetal harm.

The assessment of drug risk vs benefit in critically ill pregnant women is particularly complicated since potential delays in therapy could lead to adverse outcomes for the mother and fetus. Often initial life-saving interventions are performed without knowing whether or not a critically ill woman is pregnant. There is a saying that as maternal health goes, so goes fetal health^[24]. Recommendations by the American College of Obstetricians and Gynecologists specifically state that necessary medications should not be withheld to due to fetal concerns^[25]. Usually, there are at least a few potential alternatives in which case the decision is made based on factors such as drug risk category, other drug toxicities and experience with the drug in pregnancy. The two examples of severe sepsis/septic shock and hypertensive crisis will be used to illustrate some of these considerations. In general, the recommendations for fluids, vasoactive agents, and antimicrobial agents in pregnant women with severe sepsis or septic shock are the same as for non-pregnant women^[26,27]. In fact, the recommendations in the Surviving Sepsis Guidelines have been endorsed by respected organizations such as the Royal College of Obstetricians and Gynaecologists^[28]. Prior to widespread endorsement of these guidelines, arguments for the use of specific agents such as choice of vasopressors was often made on the basis of animal models that focused on issues such as uterine blood

flow^[29]. Current thinking is that the potential mortality benefits of optimal resuscitation with a more potent agent such as norepinephrine outweigh more local or regional blood flow concerns^[26]. In cases where there is no clear drug of choice, as might occur with antimicrobial selection, drugs with well-described toxicities (e.g., aminoglycoside nephrotoxicity) should only be prescribed when similarly efficacious, but less toxic agents are not an option (as should be the case in non-pregnant women).

In contrast to severe sepsis and septic shock that have one widely accepted guideline with treatment recommendations aimed at reducing mortality, there are multiple guidelines and recommended agents for treating hypertensive crisis during pregnancy. There is no high level evidence to suggest any differences in antihypertensive agents using mortality as the outcome of interest, so the choice-of-drug decision is heavily based on toxicity considerations. In the past, IV hydralazine was routinely recommended as a first-line choice for hypertensive crises including preeclampsia, but it is increasingly being considered a second-tier agent^[30,31]. Currently, IV labetalol is considered as a preferred first-line agent for hypertensive crisis in pregnant women in the majority of treatment guidelines^[32], but alternatives exist for refractory cases as long as one considers potential toxicities especially with more prolonged use (e.g., methemoglobinemia due to nitroglycerin)^[33,34]. An example of a class of antihypertensive agents that should almost always be avoided during pregnancy is the angiotensin-converting enzyme inhibitors such as intravenous enalaprilat that have a boxed warning about potential fetal injury and death when given during the second and third trimesters of pregnancy.

There are far more questions than answers when it comes to supportive care drug (e.g., analgesics, sedatives) use in the critically ill pregnant patient, and the risk/benefit assessment must include potential harm to the fetus. The difficulty in such assessments is illustrated by the choice of a sedative agent for a pregnant critically ill patient. In the not too distant past, benzodiazepines were the drugs of choice for ICU sedation. However, benzodiazepines cross the placenta and are labeled as pregnancy category D. Additionally, alternative sedative agents are now available including propofol (category B) and dexmedetomidine (category C), but there is little data on longer-term use in pregnant women. This can lead to difficult decisions in pregnant women with prolonged ICU stays^[35]. Table 9 lists some of the more common drugs used in the ICU setting and their implications for use in pregnant women. This table is meant to supplement other materials including more specific recommendations in FDA-approved product information brochures (e.g., the use of preservative-free heparin and low molecular weight heparin preparations).

Recommendations

The drug management principles for critically ill pregnant

patients are the same as for non-pregnant patients in the sense that potentially life-saving medications should not be withheld when no similarly efficacious therapies exist. When the situation is less dire and when more than one drug option is available, the benefit vs risk assessment should take into account the limited information on potential maternal/fetal harm that is available. Some decisions will be more clear-cut than others. For example, there are multiple agents available for treating hypertensive episodes in the ICU, so there would rarely if ever be a need to use sustained dosing with an agent like an ACE-inhibitor that has documented potential for fetal harm. For more difficult therapeutic dilemmas, additional expertise such as that by genetic counseling experts may be helpful.

Drug choice or dosing in extracorporeal membrane oxygenation

Long-term ECMO was first used in an adult patient with respiratory failure in 1972, but initial enthusiasm was dampened when a randomized trial of ECMO for adult respiratory distress syndrome (ARDS) was stopped due to futility^[36]. Enthusiasm for this technique has been renewed based on reductions in mortality noted in more recent randomized and cohort studies of patients with severe ARDS, and in particular, H1N1-related ARDS^[37,38]. From a medication standpoint, much of the emphasis has been on anticoagulation strategies and monitoring, which is not surprising given that bleeding and thrombosis are important causes of ECMO-associated morbidity and mortality^[39]. However, ECMO may also alter the pharmacokinetic, pharmacodynamics and therapeutic properties of medications that must be administered to patients receiving this modality - that is the focus of this discussion. One recent review of pharmacokinetic changes associated with ECMO concluded that "published literature is insufficient to make any meaningful recommendations for adjusting therapy for drug dosing"^[40]. Fortunately, there are ongoing systematic studies that are investigating the actions of a variety of drugs commonly administered during ECMO procedures^[41,42]. The studies involving drug administration in conjunction with ECMO fall into 3 general categories: *in vitro* studies related to physicochemical properties of drugs (e.g., drug binding to ECMO circuitry); pharmacokinetic studies; and clinical trials. The *in vitro* studies are demonstrated by a recent investigation that evaluated potential drug sequestration in ECMO circuitry by 5 drugs commonly administered to critically ill patients. Equivalent doses of 2 opioids (fentanyl, morphine), 1 sedative (midazolam), and 2 antimicrobials (meropenem, vancomycin) were studied in ECMO circuits and polyvinylchloride jars with fresh human whole blood^[43]. There were no substantial issues of stability or sequestration with vancomycin or morphine, but meropenem recovery was low (20% vs 42% in ECMO vs control, respectively) suggesting temperature-related stability issues, and fentanyl and midazolam recovery were significantly lower in the

Table 9 Implications of medications for the pregnant critically ill patient

Indication/class	Specific drug	FDA ³	Comments ¹	Indication/class	Specific drug	FDA ³	Comments ¹	
Sedative	Propofol	B	Risk (1 st and 3 rd trimesters)	Anticoagulant	Enoxaparin	B	Data suggest risk	
	Midazolam	D			Heparin	C		
	Lorazepam	D			Fondaparinux	B		
	Dexmedetomidine	C			Argatroban	B		
Analgesic	Morphine	C	Risk (3 rd trimester)	Corticosteroid	Methylprednisolone	C	Data suggest risk	
	Fentanyl	C			Hydrocortisone	C		
	Hydromorphone	C			Antifungal/ antiviral	Voriconazole		D
Delirium	Quetiapine	C	Risk (1 st and 3 rd trimesters)		Fluconazole	D	Data suggest risk if > 400 mg/d	
Pulmonary hypertension	Haloperidol	C	Antibiotic		Micafungin	C	Data suggest low risk	
	Epoprostenol	B			Amphotericin	B		
	Treprostinil	B			Acyclovir	B		
Bronchodilator	Iloprost	C			Azithromycin	B		
	Tiotropium	C			Aztreonam	B		
	Ipratropium	B			Cefazolin	B		
Vasoactive	Albuterol	B			Cefepime	B		
	Levalbuterol	C			Cefoxitin	B		
	Epinephrine	C		Data suggest risk	Ceftriaxone	B		
	Norepinephrine	C		Data suggest risk	Ciprofloxacin	C		
	Vasopressin	C			Clindamycin	B		
	Phenylephrine	C		Data suggest risk	Linezolid	C		
	Dopamine	C			Meropenem	B		
Antiarrhythmic	Dobutamine	B			Metronidazole	B		Data suggest low risk
	Milrinone	C			Moxifloxacin	C		Data suggest low risk
	Diltiazem	C	Data suggest low risk		Piperacillin/ tazobactam	B		
	Antihypertensive	Amiodarone	D	Data suggest risk	Anti-seizure ²	Vancomycin	C	
Digoxin		C		Levetiracetam		C		
Labetalol		C	Data suggest low risk	Paralytic	Phenytoin	D		
Esmolol		C			Rocuronium	C		
Hydralazine	C	Risk (3 rd trimester)	Cisatracurium		B			
Magnesium sulfate	D		Vecuronium		C			
Nitroglycerin	C	Data suggest low risk	Succinylcholine		C			
Sodium nitroprusside	C	Data suggest risk						
Diuretic	ACE-inhibitors	D	Data suggest risk (2 nd and 3 rd trimesters)					
	Furosemide	C	Data suggest low risk					
	Mannitol	C						
GI/antiemetic	Pantoprazole	B	Data suggest low risk					
	Famotidine	B						
	Ondansetron	B						
	Metoclopramide	B						
	Erythromycin (non-estolate)	B						

¹Human data to suggest risk based on data from Briggs *et al*^[23]; ²Pregnant women exposed to AEDs should register with the North American Antiepileptic Drug Pregnancy Registry (888-233-2334); ³Refers to FDA pregnancy rating category. FDA: Food and Drug Administration; ACE: Angiotensin converting enzyme.

ECMO groups (3% vs 82%, $P = 0.0005$ and 13% vs 100%, $P = 0.01$, respectively) suggesting lipophilic-drug sequestration. Dosing modifications based on these *ex-vivo* findings of meropenem instability requires further study, but there are potential implications for other thermo-labile medications. In contrast to these findings that suggest no stability or sequestration concerns with morphine, another *in vitro* study found that 40% of a single dose of morphine was removed by ECMO tubing or circuitry^[44]. The differences in morphine disposition in these 2 studies may be a function of differing methodologies, but they illustrate the problem with excessive reliance on *in vitro* data.

Pharmacokinetic studies have the potential advantage

of measuring blood drug concentrations *in vivo* but these studies require the availability of a drug assay, presume a relationship between a surrogate marker (*i.e.*, the blood concentration of the drug or its active metabolite) and therapeutic effect, and are difficult to perform in critically ill patients. Pharmacokinetic studies are commonly employed for investigations of antimicrobial agents used to treat infections associated with ECMO. For example, antiviral medications have been used in combination with ECMO for treating severe influenza infections. Pharmacokinetic studies involving the neuraminidase inhibitor oseltamivir given enterally in critically ill adult patients on ECMO suggest that normal doses of oseltamivir (*i.e.*, 75 mg twice daily) are appropriate

Table 10 Drug dosing considerations in adult patients receiving extracorporeal membrane oxygenation

Drug dosing recommendations for an adult on ECMO are unlikely to be evidenced-based
Data from neonatal case reports, case series or studies may not apply to adults
Data from one drug may not be applicable to another even from the same class
Drug regimen recommendations in critical care guidelines may not apply to patients on ECMO
Organ dysfunction apart from the lung and heart complicate interpretation of literature
The contribution of distinct physicochemical properties of drugs to sequestration is unclear
Hydrophilicity or lipophilicity appear to be important factors affecting pharmacokinetics
The therapeutic actions of drugs are not consistently predictable by pharmacokinetics
The design and properties of the equipment change over time with implications for dosing
The priming solution such as blood or blood-derived products may affect dosing

ECMO: Extracorporeal membrane oxygenation.

unless a patient has concomitant renal dysfunction in which case dose reduction may be in order^[45-47]. Case report pharmacokinetic data in patients undergoing ECMO is available for other antimicrobials including the antifungal agents caspofungin and voriconazole^[48]. Similar to pharmacokinetic studies, there are a few studies using laboratory parameters as surrogate markers of clinical effect. For example, in critically ill patients on ECMO who were receiving argatroban for suspected heparin-induced thrombocytopenia, argatroban requirements based on activated partial thromboplastin time monitoring were found 10-fold lower than the 2 µg/kg per minute dose recommended in product labeling^[49].

There are limited clinical studies involving drug choice or dosing in patients undergoing ECMO and the data from these studies does not always seem to corroborate data from the *in vitro* and pharmacokinetic investigations. For example, one retrospective study found that morphine and midazolam requirements increased, but fentanyl requirements remained unchanged with continued dosing over time in adult patients on ECMO for cardiorespiratory failure^[50]. On the other hand, neonates on ECMO required less supplemental analgesia when given morphine infusions vs fentanyl infusions in a historical control group^[51]. The patients in the morphine group all experienced less withdrawal and were discharged earlier ($P = 0.01$ for both). Table 10 lists some of the more important considerations when evaluating published literature and devising dosing regimens in critically ill patients receiving ECMO.

Recommendations

The paucity of literature regarding drug dosing in ECMO with relevant clinical outcomes precludes any meaningful evidence-based recommendations. Therefore, the clinician must extrapolate information from the limited *ex vivo* and pharmacokinetic studies that have been conducted for selected drugs taking into account changes in ECMO technologies in recent years that may influence previous study findings. *Ex vivo* studies suggest that lipophilic drugs are particularly prone sequestration by ECMO circuitry. For drugs titrated to clinical effect such as opioids, the clinician may either choose to use less lipophilic agents such as morphine (assuming no renal failure) or use more lipophilic agents like fentanyl with the appreciation that higher than expected doses may

be needed. For some drugs, therapeutic drug monitoring may be available and useful. For lipophilic or thermolabile (e.g., carbapenems and ampicillin) drugs that are not titrated to clinical effect and for which therapeutic drug monitoring is usually not available, the clinician must be alert for potential therapeutic unresponsiveness or failure due to inadequate dosing. Table 11 lists the pharmacokinetic and physicochemical characteristics of drugs commonly used in critically ill patients in order to help with drug selection and dosing when data from clinical trials involving ECMO are not available.

Drug choice or dosing during plasma exchange

Plasma exchange (aka plasmapheresis) is another modality that has drug-dosing related concerns. If one assumes a normal plasma volume of approximately 4 L for an 80 kg patient, then plasma exchange at a rate of approximately 50 mL/kg over 2 h would remove 2 plasma volumes and more than 80% of all solutes^[52]. Much of the experience with plasma exchange has been case report data associated with overdosing or poisonings. The AABB and the American Society for Apheresis has concluded that there is little or conflicting evidence for the latter indications and that such use represents "heroic" or "last-ditch" efforts^[53]. Apart from the intended use of plasma exchange for toxicological problems, there is the unintended effect of plasma exchange on drugs being used in usual therapeutic doses.

Drugs most likely to be eliminated by plasma exchange are those with small volumes of distribution that approximate extracellular fluid stores (less than 0.2 L/kg) and those with plasma protein binding of at least 80%^[54]. Since plasma proteins and bound drugs are removed in tandem with fluid in plasma exchange, there is increased drug removal with increased protein binding in contrast to hemodialysis that preferentially removes unbound drugs. The timing of drug administration relative to onset of plasma exchange is critical to the amount of drug elimination. Hydrophilic drugs with small volumes of distribution and high protein binding would be particularly susceptible to removal if initiated after plasma exchange has begun. Lipophilic drugs with larger volumes of distribution would not be expected to have substantial removal by plasma exchange, presuming

Table 11 Pharmacokinetic and physicochemical properties of drugs commonly used in the intensive care units¹

Indication/class	Specific drug	LogP	Pb (%)	Vd (L/kg)
Sedative	Propofol	4.16	98	60
	Midazolam	3.33	97	2
	Lorazepam	3.53	91	1.3
	Dexmedetomidine	3.39	94	1.3
Analgesic	Morphine	0.9	35	3
	Fentanyl	3.82	83	5
	Hydromorphone	1.62	20	1.2
Delirium	Quetiapine	2.81	83	10
	Haloperidol	3.66	92	18
Antiarrhythmic	Diltiazem	2.37	80	5
	Amiodarone	7.64	98	70
	Digoxin	2.37	25	6
Antihypertensive	Labetalol	1.89	50	5
	Esmolol	1.82	55	3
	Hydralazine	0.75	87	4
GI/antiemetic	Pantoprazole	2.18	98	0.15
	Famotidine	-2	18	1.2
	Ondansetron	2.35	73	2
	Metoclopramide	1.4	30	4.4
	Erythromycin	2.6	85	0.6
Anticoagulant	Enoxaparin	-8.3	80	0.07
	Heparin	NA	NA	0.05
	Fondaparinux	-10	94	0.1
	Argatroban	-0.97	54	0.17
Corticosteroid	Methylprednisolone	1.56	78	1.1
	Hydrocortisone	1.28	95	0.5
Antifungal/ antiviral	Voriconazole	1.82	58	3
	Fluconazole	0.56	11	0.8
	Micafungin	-6.3	99	0.39
	Amphotericin	-2.3	95	1.8
	Acyclovir	-1	9-33	0.6
Antibiotic	Azithromycin	2.44	51	0.44
	Aztreonam	-3.1	56	0.17
	Cefazolin	-1.5	80	0.14
	Cefepime	-4.3	20	0.23
	Cefoxitin	0.29	75	0.26
	Ceftriaxone	-1.8	95	0.14
	Ciprofloxacin	-0.81	35	2.5
	Clindamycin	1.04	93	2.5
	Linezolid	0.64	31	0.64
	Meropenem	-4.4	2	0.36
	Metronidazole	-0.46	25	1
	Moxifloxacin	-0.5	50	2
	Piperacillin/ tazobactam	-0.26		0.1
	Vancomycin	-3.1	55	0.7
Anti-seizure	Levetiracetam	-0.59	8	0.6
	Phenytoin	2.15	90	0.7

¹LogP is the octanol-water partition coefficient and is expressed as the ratio of the solubility of a compound in octanol (non-polar solvent) to its solubility in water (polar solvent). Some of the data from this table (particularly the log P values) were obtained from www.drugbank.ca. NA: Not applicable.

the plasma exchange is not initiated until after the initial distribution phase of the drug has taken place. There is case report data for some drugs that confirm these generalizations. For example, voriconazole that has a volume of distribution slightly over 4 L/kg and protein binding of approximately 58% would not be expected to have significant removal by plasma exchange and this was confirmed in a pharmacokinetic study involving a patient receiving plasma exchange in conjunction with voriconazole for an invasive aspergillosis infection^[55].

Recommendations

Once it is known that a patient will undergo plasma exchange, the clinician must evaluate each of the drugs being administered to the patient and attempt to devise an optimal dosing regimen or find alternative drugs unlikely to be affected by the procedure (*i.e.*, large volume of distribution and low protein binding). The evaluation must take into account the specific plasma expander being used as a replacement fluid, since albumin or albumin-containing fluids like fresh frozen plasma influence drug binding. Additionally, the evaluation should consider the pharmacokinetics of the drug, the timing of the drug relative to the plasma exchange procedure, co-morbidities such as renal failure that might alter normal kinetics, and the limited published literature that is available. Table 11 lists pharmacokinetic and physicochemical properties of drugs commonly used in critically ill patients that can be used to help predict drug disposition in association with plasma exchange.

CONCLUSION

Special populations of ICU patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

REFERENCES

- 1 Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Med* 2004; **30**: 18-32 [PMID: 14625670 DOI: 10.1111/j.1365-2125.2011.04159.x]
- 2 Godoy R, Goodman E, Levins R, Leonard WR. Anthropometric variability in the USA: 1971-2002. *Ann Hum Biol* 2005; **32**: 469-486 [PMID: 16147396 DOI: 10.1080/03014460500154384]
- 3 Thibault R, Genton L, Pichard C. Body composition: why, when and for who? *Clin Nutr* 2012; **31**: 435-447 [PMID: 22296871 DOI: 10.1016/j.clnu.2011.12.011]
- 4 Heysfield SB, Thomas D, Bosy-Westphal A, Shen W, Peterson CM, Müller MJ. Evolving concepts on adjusting human resting energy expenditure measurements for body size. *Obes Rev* 2012; **13**: 1001-1014 [PMID: 22863371 DOI: 10.1111/j.1467-789X.2012.01019.x]
- 5 Jain R, Chung SM, Jain L, Khurana M, Lau SW, Lee JE, Vaidyanathan J, Zadezensky I, Choe S, Sahajwalla CG. Implications of obesity for drug therapy: limitations and challenges. *Clin Pharmacol Ther* 2011; **90**: 77-89 [PMID: 21633345 DOI: 10.1038/

- clpt.2011.104]
- 6 **Heymsfield SB**, Gonzalez MC, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes Rev* 2014; **15**: 310-321 [PMID: 24447775 DOI: 10.1111/obr.12143]
- 7 **Chechi K**, Nedergaard J, Richard D. Brown adipose tissue as an anti-obesity tissue in humans. *Obes Rev* 2014; **15**: 92-106 [PMID: 24165204 DOI: 10.1111/obr.12116]
- 8 **Akinnusi ME**, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. *Crit Care Med* 2008; **36**: 151-158 [PMID: 18007266 DOI: 10.1097/01.CCM.0000297885.60037.6E]
- 9 **Pickkers P**, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. *Crit Care Med* 2013; **41**: 1878-1883 [PMID: 23685638 DOI: 10.1097/CCM.0b013e31828a2aa1]
- 10 **Jensen GL**, Friedmann JM, Henry DK, Skipper A, Beiler E, Porter C, Boyd-Kantoff D. Noncompliance with body weight measurement in tertiary care teaching hospitals. *JPEN J Parenter Enteral Nutr* 2003; **27**: 89-90 [PMID: 12549605 DOI: 10.1177/014860710302700189]
- 11 **Anastasio P**, Spitali L, Frangiosa A, Molino D, Stellato D, Cirillo E, Pollastro RM, Capodicasa L, Sepe J, Federico P, Gaspare De Santo N. Glomerular filtration rate in severely overweight normotensive humans. *Am J Kidney Dis* 2000; **35**: 1144-1148 [PMID: 10845829 DOI: 10.1016/S0272-6386(00)70052-7]
- 12 **Demirovic JA**, Pai AB, Pai MP. Estimation of creatinine clearance in morbidly obese patients. *Am J Health Syst Pharm* 2009; **66**: 642-648 [PMID: 19299371 DOI: 10.2146/ajhp080200]
- 13 **Udy AA**, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, Boots RJ, Lipman J. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations*. *Crit Care Med* 2014; **42**: 520-527 [PMID: 24201175 DOI: 10.1097/CCM.0000000000000029]
- 14 **Jacques KA**, Erstad BL. Availability of information for dosing injectable medications in underweight or obese patients. *Am J Health Syst Pharm* 2010; **67**: 1948-1950 [PMID: 21048212 DOI: 10.2146/ajhp100226]
- 15 **Erstad BL**. Drug Dosing in the Critically Ill Obese Patient. El Solh AA, editor. *Critical Care Management of the Obese Patient*. Hoboken, NJ: John Wiley & Sons, Ltd, 2012: 197-207 [DOI: 10.1002/9781119962083.ch22]
- 16 **Brown DL**, Masselink AJ, Lalla CD. Functional range of creatinine clearance for renal drug dosing: a practical solution to the controversy of which weight to use in the Cockcroft-Gault equation. *Ann Pharmacother* 2013; **47**: 1039-1044 [PMID: 23757387 DOI: 10.1345/aph.1S176]
- 17 **Feldschuh J**, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation* 1977; **56**: 605-612 [PMID: 902387]
- 18 **Lemmens HJ**, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. *Obes Surg* 2006; **16**: 773-776 [PMID: 16756741 DOI: 10.1381/096089206777346673]
- 19 **Osterkamp LK**. Current perspective on assessment of human body proportions of relevance to amputees. *J Am Diet Assoc* 1995; **95**: 215-218 [PMID: 7852688 DOI: 10.1016/S0002-8223(95)00050-X]
- 20 **Pollock W**, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. *Intensive Care Med* 2010; **36**: 1465-1474 [PMID: 20631987 DOI: 10.1007/s00134-010-1951-0]
- 21 **Brown S**, Mozurkewich E. Trauma during pregnancy. *Obstet Gynecol Clin North Am* 2013; **40**: 47-57 [PMID: 23466136 DOI: 10.1016/j.ogc.2012.11.004]
- 22 **Ramoz LL**, Patel-Shori NM. Recent changes in pregnancy and lactation labeling: retirement of risk categories. *Pharmacotherapy* 2014; **34**: 389-395 [PMID: 24390829 DOI: 10.1002/phar.1385]
- 23 **Briggs GG**, Freeman RK, Yaffe SJ, editors. *Drugs in Pregnancy and Lactation*. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2011
- 24 **Morgan J**, Roberts S. Maternal sepsis. *Obstet Gynecol Clin North Am* 2013; **40**: 69-87 [PMID: 23466138 DOI: 10.1016/j.ogc.2012.11.007]
- 25 **American College of Obstetricians and Gynecologists (ACOG)**. Critical care in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG), 2009: 100
- 26 **Barton JR**, Sibai BM. Severe sepsis and septic shock in pregnancy. *Obstet Gynecol* 2012; **120**: 689-706 [PMID: 22914482 DOI: 10.1097/AOG.0b013e318263a52d]
- 27 **Galvagno SM**, Camann W. Sepsis and acute renal failure in pregnancy. *Anesth Analg* 2009; **108**: 572-575 [PMID: 19151289 DOI: 10.1213/ane.0b013e3181937b7e]
- 28 **Bamfo JE**. Managing the risks of sepsis in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2013; **27**: 583-595 [PMID: 23639681 DOI: 10.1016/j.bpobgyn.2013.04.003]
- 29 **Ko R**, Mazur JE, Pastis NJ, Chang E, Sahn SA, Boylan AM. Common problems in critically ill obstetric patients, with an emphasis on pharmacotherapy. *Am J Med Sci* 2008; **335**: 65-70 [PMID: 18195587 DOI: 10.1097/MAJ.0b013e31815f1e14]
- 30 **Brown CM**, Garovic VD. Drug treatment of hypertension in pregnancy. *Drugs* 2014; **74**: 283-296 [PMID: 24554373 DOI: 10.1007/s40265-014-0187-7]
- 31 **Magee LA**, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003; **327**: 955-960 [PMID: 14576246 DOI: 10.1136/bmj.327.7421.95]
- 32 **Al Khaja KA**, Sequeira RP, Alkhaja AK, Damanhori AH. Drug treatment of hypertension in pregnancy: a critical review of adult guideline recommendations. *J Hypertens* 2014; **32**: 454-463 [PMID: 24384846 DOI: 10.1097/HJH.0000000000000069]
- 33 **Munnur U**, Bandi V, Guntupalli KK. Management principles of the critically ill obstetric patient. *Clin Chest Med* 2011; **32**: 53-60, viii [PMID: 21277449 DOI: 10.1016/j.ccm.2010.10.003]
- 34 **Neligan PJ**, Laffey JG. Clinical review: Special populations--critical illness and pregnancy. *Crit Care* 2011; **15**: 227 [PMID: 21888683 DOI: 10.1186/cc10256]
- 35 **Tajchman SK**, Bruno JJ. Prolonged propofol use in a critically ill pregnant patient. *Ann Pharmacother* 2010; **44**: 2018-2022 [PMID: 21062907 DOI: 10.1345/aph.1P427]
- 36 **Gattinoni L**, Carlesso E, Langer T. Clinical review: Extracorporeal membrane oxygenation. *Crit Care* 2011; **15**: 243 [PMID: 22188792 DOI: 10.1186/cc10490]
- 37 **Peek GJ**, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374**: 1351-1363 [PMID: 19762075 DOI: 10.1016/S0140-6736(09)61069-2]
- 38 **Noah MA**, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD, Menon D, Taylor BL, Rowan KM. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; **306**: 1659-1668 [PMID: 21976615 DOI: 10.1001/jama.2011.1471]
- 39 **Oliver WC**. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth* 2009; **13**: 154-175 [PMID: 19767408 DOI: 10.1177/1089253209347384]
- 40 **Shekar K**, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care* 2012; **27**: 741.e9-741.18 [PMID: 22520488 DOI: 10.1016/j.jcrc.2012.02.013]
- 41 **Shekar K**, Fraser JF, Roberts JA. Can optimal drug dosing during ECMO improve outcomes? *Intensive Care Med* 2013; **39**: 2237 [PMID: 24037225 DOI: 10.1007/s00134-013-3080-z]
- 42 **Shekar K**, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, Ghassabian S, Wallis SC, Levkovich B, Pellegrino V, McGuinness

- S, Parke R, Gilder E, Barnett AG, Walsham J, Mullany DV, Fung YL, Smith MT, Fraser JF. ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation: a multi-centre study to optimise drug therapy during ECMO. *BMC Anesthesiol* 2012; **12**: 29 [PMID: 23190792 DOI: 10.1186/1471-2253-12-29]
- 43 **Shekar K**, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, Ghassabian S, Wallis SC, Fung YL, Smith MT, Fraser JF. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. *Crit Care* 2012; **16**: R194 [PMID: 23068416 DOI: 10.1186/cc11679]
- 44 **Tong H**, Chen W, Steenberg C, Murphy E. Ischemic preconditioning activates phosphatidylinositol-3-kinase upstream of protein kinase C. *Circ Res* 2000; **87**: 309-315 [PMID: 10948065 DOI: 10.1191/0267659105pf8270a]
- 45 **Mulla H**, Peek GJ, Harvey C, Westrope C, Kidy Z, Ramaiah R. Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support. *Anaesth Intensive Care* 2013; **41**: 66-73 [PMID: 23362894]
- 46 **Eyler RF**, Heung M, Pleva M, Sowinski KM, Park PK, Napolitano LM, Mueller BA. Pharmacokinetics of oseltamivir and oseltamivir carboxylate in critically ill patients receiving continuous venovenous hemodialysis and/or extracorporeal membrane oxygenation. *Pharmacotherapy* 2012; **32**: 1061-1069 [PMID: 23208833 DOI: 10.1002/phar.1151]
- 47 **Kromdijk W**, Sikma MA, van den Broek MP, Beijnen JH, Huitema AD, de Lange DW. Pharmacokinetics of oseltamivir carboxylate in critically ill patients: each patient is unique. *Intensive Care Med* 2013; **39**: 977-978 [PMID: 23443310 DOI: 10.1007/s00134-013-2851-x]
- 48 **Spriet I**, Annaert P, Meersseman P, Hermans G, Meersseman W, Verbesselt R, Willems L. Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *J Antimicrob Chemother* 2009; **63**: 767-770 [PMID: 19218271 DOI: 10.1093/jac/dkp026]
- 49 **Beiderlinden M**, Treschan T, Görlinger K, Peters J. Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; **31**: 461-465 [PMID: 17537058 DOI: 10.1111/j.1525-1594.2007.00388.x]
- 50 **Shekar K**, Roberts JA, Mullany DV, Corley A, Fisquet S, Bull TN, Barnett AG, Fraser JF. Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. *Anaesth Intensive Care* 2012; **40**: 648-655 [PMID: 22813493]
- 51 **Franck LS**, Vilardi J, Durand D, Powers R. Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. *Am J Crit Care* 1998; **7**: 364-369 [PMID: 9740886]
- 52 **Ibrahim RB**, Liu C, Cronin SM, Murphy BC, Cha R, Swerdlow P, Edwards DJ. Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy* 2007; **27**: 1529-1549 [PMID: 17963462 DOI: 10.1592/phco.27.11.1529]
- 53 **Smith JW**, Weinstein R, Hillyer KL. Therapeutic apheresis: a summary of current indication categories endorsed by the AABB and the American Society for Apheresis. *Transfusion* 2003; **43**: 820-822 [PMID: 12757535 DOI: 10.1046/j.1537-2995.2003.00397.x]
- 54 **Ibrahim RB**, Balogun RA. Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. *Semin Dial* 2012; **25**: 176-189 [PMID: 22321259 DOI: 10.1111/j.1525-139X.2011.01030.x]
- 55 **Spriet I**, Brüggemann RJ, Annaert P, Meersseman P, Van Wijngaerden E, Lagrou K, Willems L. Pharmacokinetic profile of voriconazole in a critically ill patient on therapeutic plasma exchange. *Ther Drug Monit* 2013; **35**: 141-143 [PMID: 23296095 DOI: 10.1097/FTD.0b013e31827d76b0]
- 56 **Erstad BL**. Special Caveats of Drugs Used in Critical Care Medicine. In: Roberts PR, Todd SR, editors. *Comprehensive Critical Care: Adult*. Mount Prospect, IL: Society of Critical Care Medicine, 2012: 779-789
- 57 **Erstad BL**. Medication Dosing in Overweight and Obese Patients. In: Murphy JE, editor. *Clinical Pharmacokinetics*. 5th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2012: 27

P- Reviewer: Ciccone MM, Kanda T, Tamemoto H
S- Editor: Tian YL **L- Editor:** A **E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Critical Care Medicine*

World J Crit Care Med 2015 August 4; 4(3): 152-264



Editorial Board

2011-2015

The *World Journal of Critical Care Medicine* Editorial Board consists of 246 members, representing a team of worldwide experts in critical care medicine. They are from 45 countries, including Argentina (2), Australia (8), Austria (2), Bangladesh (1), Belgium (3), Brazil (4), Canada (7), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (8), Germany (11), Greece (9), Hungary (1), India (10), Iran (2), Ireland (1), Israel (6), Italy (14), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (3), Singapore (1), Slovenia (1), South Africa (1), Spain (7), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (8), United States (72), and Uruguay (1).

EDITOR-IN-CHIEF

Yaseen Mohamed Arabi, *Riyadh*

GUEST EDITORIAL BOARD MEMBERS

Hsing I Chen, *Hualien*
Sheng-Hsien Chen, *Tainan*
Yih-Sharnng Chen, *Taipei*
Yung-Chang Chen, *Taipei*
Der-Yang Cho, *Taichung*
Cheng-Keng Chuang, *Taoyuan*
How-Ran Guo, *Tainan*
Bang-Gee Hsu, *Hualien*
Chien-Wei Hsu, *Kaohsiung*
Wen-Jinn Liaw, *Taipei*
Yan-Ren Lin, *Changhua*
Jiunn-Jye Sheu, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Eduardo Chuluyan, *Buenos Aires*
Adrian Angel Inchauspe, *Berazategui*



Australia

Zsolt J Balogh, *Newcastle*
Zoltan Huba Endre, *Sydney*
Nam Q Nguyen, *Adelaide*
Alistair D Nichol, *Melbourne*
Srinivas Rajagopala, *Adelaide*
Georg Marcus Schmolzer, *Melbourne*
Andrew Trevitt Slack, *Southport*
Ravindranath Tiruvoipati, *Frankston*



Austria

Lars-Peter Kamolz, *Vienna*
Sylvia Knapp, *Vienna*



Bangladesh

Saidur Rahman Mashreky, *Dhaka*



Belgium

Teresinha Leal, *Brussels*
Manu Malbrain, *Antwerp*
Jean-Louis Vincent, *Brussels*



Brazil

Luciano CP Azevedo, *São Paulo*
Patricia Rieken Macedo Rocco, *Rio de Janeiro*
Marcos Antonio Rossi, *São Paulo*
Renato Seligman, *Porto Alegre*



Canada

Douglas D Fraser, *London*
Pierre A Guertin, *Quebec*
Marc Jeschke, *Toronto*
Constantine J Karvellas, *Edmonton*
Wolfgang Michael Kuebler, *Toronto*
Mingyao Liu, *Toronto*
Xi Yang, *Manitoba*



China

Xiang-Dong Chen, *Chengdu*

Xu-Lin Chen, *Hefei*
Wong Tak Chuen, *Hong Kong*
Ming-Xu Da, *Gansu*
Huang-Xian Ju, *Nanjing*
Ting-Bo Liang, *Hangzhou*
Peng-Lin Ma, *Beijing*
Chung-Wah David Siu, *Hong Kong*
Yong-Ming Yao, *Beijing*
Jia-Ping Zhang, *Chongqing*
Wei-Dong Zhou, *Beijing*



Croatia

Alan Sustic, *Rijeka*



Cuba

Jesús Pérez-Nellar, *La Habana*



Denmark

Dan Stieper Karbing, *Aalborg*



Egypt

Ibrahim Abouomira, *Cairo*
Hanan Ibrahim, *Cairo*
Amr M Moghazy, *Alexandria*
Ayman A Yousef, *Tanta*



Finland

Asko Armas Riutta, *Tampere*

**France**

Jean-Marc Cavaillon, *Paris*
 Jean-Michel Constantin, *Clermont-Ferrand*
 Marc Leone, *Marseille*
 Bruno Mégarbane, *Paris*
 Saad Nseir, *Lille*
 Nicolas Terzi, *Caen*
 Jean-François Timsit, *La Tronche Cedex*
 Benoit Vallet, *Lille*

**Germany**

Hendrik Bracht, *Ulm*
 Michael Czaplik, *Aachen*
 Gerrit Grieb, *Aachen*
 Tobias Keck, *Freiburg*
 Philipp Kobbe, *Aachen*
 Alexander Koch, *Aachen*
 Marc Maegele, *Cologne*
 Norbert Pallua, *Aachen*
 Andrzej Antoni Piatkowski, *Aachen*
 Armin Rudolf Sablotzki, *Leipzig*
 Kai D Zacharowski, *Frankfurt am Main*

**Greece**

Ioanna Dimopoulou, *Athens*
 Dimitrios Karakitsos, *Athens*
 Petros Kopterides, *Athens*
 Gregory Kouraklis, *Athens*
 Athanasios D Marinis, *Athens*
 George Nakos, *Ioannina*
 Papaioannou E Vasilios, *Alexandroupolis*
 Theodoros Xanthos, *Athens*
 Spyros G Zakyntinos, *Athens*

**Hungary**

Zoltan Rakonczay, *Szeged*

**India**

Rachna Agarwal, *Delhi*
 Ritesh Agarwal, *Chandigarh*
 Mohammad Farooq Butt, *Srinagar*
 Mohan Gurjar, *Lucknow*
 Deven Juneja, *New Delhi*
 Farhad N Kapadia, *Mumbai*
 Vikram Kate, *Pondicherry*
 Pramod Kumar, *Manipal*
 Ritesh G Menezes, *Mangalore*
 Medha Mohta, *Delhi*

**Iran**

Hemmat Maghsoudi, *Tabriz*
 Homayoun Sadeghi-Bazargani, *Tabriz*

**Ireland**

Sanjay H Chotirmall, *Dublin*

**Israel**

Alexander Becker, *Kefar Tavor*
 Yoram Kluger, *Haifa*
 Yona Kosashvili, *Zerrifin*
 Kobi Peleg, *Tel Aviv*
 Ilan Sela, *Rehovot*
 Pierre Singer, *Tel Aviv*

**Italy**

Giacomo Bellani, *Monza*
 Giovanni Camussi, *Torino*
 Anselmo Caricato, *Rome*
 Piero Ceriana, *Pavia*
 Antonio Chiaretti, *Rome*
 Davide Chiumello, *Milano*
 Alfredo Conti, *Messina*
 Paolo Cotogni, *Torino*
 Daniele M De Luca, *Rome*
 Vincenzo De Santis, *Rome*
 Luca La Colla, *Parma*
 Giovanni Landoni, *Milano*
 Raffaele Scala, *Lucca*
 Giovanni Vento, *Rome*

**Japan**

Keishiro Aoyagi, *Kurume*
 Satoshi Hagiwara, *Yufu*
 Yuichi Hattori, *Toyama*
 Hideo Inaba, *Kanazawa*
 Eisuke Kagawa, *Hiroshima*
 Chieko Mitaka, *Tokyo*

**Jordan**

Feras Ibrahim Hawari, *Amman*

**Mexico**

Silvio A Ñamendys-Silva, *Mexico City*

**Morocco**

Redouane Abouqal, *Rabat*

**Netherlands**

WA Buurman, *Maastricht*
 Martin CJ Kneyber, *Groningen*
 Patrick Schober, *Amsterdam*
 Arie Barend Van Vugt, *Enschede*

**New Zealand**

Sultan Zayed Al-Shaqsi, *Dunedin*
 Arman Adam Kahokehr, *Whangarei*
 John William Pickering, *Christchurch*

**Norway**

Ulf R Dahle, *Oslo*

**Poland**

Maciej Owecki, *Poznań*

**Portugal**

Ernestina Rodrigues Gomes, *Porto*
 Cristina Granja, *Porto*
 José António Lopes, *Lisbon*
 Pedro M Póvoa, *Lisbon*

**Russia**

Konstantin A Popugaev, *Moscow*

**Saudi Arabia**

Imran Khalid, *Jeddah*
 Mohamed Taifour Suliman, *Tabuk*

**Singapore**

Devanand Anantham, *Singapore*

**Slovenia**

Štefek Grmec, *Maribor*

**South Africa**

DL Clarke, *Pietermaritzburg*

**Spain**

Juan Carlos Montejo González, *Madrid*
 David Jimenez, *Madrid*
 Juan Antonio Llompарт-Pou, *Palma*
 Antonio Torres Mart, *Barcelona*
 Enrique Ariel Piacentini, *Barcelona*
 Alonso Mateos Rodriguez, *Madrid*
 R Rodríguez-Roisin, *Barcelona*

**Sweden**

Mihai Oltean, *Gothenburg*

**Switzerland**

Dieter Cadosch, *Zurich*
 Mihael Potocki, *Basel*
 John Friedrich Stover, *Zurich*

**Thailand**

Viroj Wiwanitkit, *Bangkok*

**Tunisia**

Mabrouk Bahloul, *Sfax*

**Turkey**

Yusuf Kenan Coban, *Malatya*
Bensu Karahalil, *Ankara*
Ali Nayci, *Mersin*

**United Kingdom**

Sammy Al-Benna, *Nottingham*
Giles N Cattermole, *London*
Frantisek Duska, *Nottingham*
James Nicholas Fullerton, *London*
Christina Jones, *Prescot*
Sameer Khan, *Middlesbrough*
George Ntoumenopoulos, *London*
Cecilia O'Kane, *Belfast*

**United States**

Edward Abraham, *Winston-Salem*
Bernard R Bendok, *Chicago*
Michael Blaivas, *Atlanta*

Charles D Boucek, *Pittsburgh*
Marcia Leigh Brackbill, *Winchester*
Ronald A Bronicki, *Houston*
Robert C Cantu, *Concord*
Marylou Cardenas-Turanzas, *Houston*
Archana Chatterjee, *Omaha*
Paul A Checchia, *St. Louis*
Rubin Issam Cohen, *New Hyde Park*
Stephen Cohn, *San Antonio*
Donald Edward Craven, *Burlington*
Ruy J Cruz Jr, *Pittsburgh*
Francis C Dane, *Roanoke*
Marc de Moya, *Boston*
Steven M Donn, *Ann Arbor*
Christopher P Farrell, *Wynnewood*
Marco Fernández, *Nashville*
Kevin Foster, *Phoenix*
Barry D Fuchs, *Philadelphia*
Richard P Gonzalez, *Mobile*
Kenneth W Gow, *Seattle*
Alan H Hall, *Laramie*
Jijo John, *Oklahoma City*
Lewis J Kaplan, *New Haven*
Jason N Katz, *Chapel Hill*
Salah Georges Keyrouz, *Little Rock*
Deborah A Kuhls, *Las Vegas*
Gregory Luke Larkin, *New Haven*
Christos Lazaridis, *Charleston*
James Anthony Lin, *Los Angeles*
Yahia M Lodi, *Syracuse*
Roger M Loria, *Richmond*
Aigang Lu, *Cincinnati*
Rudolf Lucas, *Augusta*
O John Ma, *Portland*
Robert T Mallet, *Fort Worth*
William T McGee, *Springfield*
Mark G McKenney, *Miami*

Michael Moussouttas, *Philadelphia*
Oliver Hans-Josef Muensterer, *Birmingham*
Rahul Nanchal, *Milwaukee*
Michael Steven Niederman, *Mineola*
Gary Frank Nieman, *Syracuse*
James Martin O'Brien, *Columbus*
Martin Oudega, *Pittsburgh*
Catherine Mobley Preissig, *Duluth*
Virginia Prendergast, *Phoenix*
Ramesh Raghupathi, *Philadelphia*
Miren Ava Schinco, *Jacksonville*
Carl Ivan Schulman, *Miami*
L Keith Scott, *Shreveport*
Kevin Navin Sheth, *Baltimore*
Jenni Short, *Salina*
Ronald Fong Sing, *Charlotte*
Philip Charles Spinella, *St. Louis*
Robert M Starke, *Charlottesville*
Stanislaw Peter A Stawicki, *Columbus*
David Christopher Stockwell, *Washington*
Stanislav Svetlov, *Gainesville*
Maged A Tanios, *Long Beach*
Neal James Thomas, *Hershey*
Nancy Moon Tofil, *Birmingham*
Balagangadhar R Totapally, *Miami*
Steven Nicholas Vaslef, *Durham*
Joseph Clark Watson, *Falls Church*
John Stephen Wilgis, *Orlando*
David Conrad Willms, *San Diego*
Haodong Xu, *Rochester*
Xiao-Ming Xu, *Indianapolis*
Midori Anne Yenari, *San Francisco*

**Uruguay**

William Manzanares, *Montevideo*

Contents

Quarterly Volume 4 Number 3 August 4, 2015

EDITORIAL

- 152 From bronchiolitis guideline to practice: A critical care perspective
Lin JA, Madikians A
- 159 Opening the doors of the intensive care unit to cancer patients: A current perspective
Ñamendys-Silva SA, Plata-Menchaca EP, Rivero-Sigarroa E, Herrera-Gómez A

REVIEW

- 163 Brain-lung crosstalk: Implications for neurocritical care patients
Mrozek S, Constantin JM, Geeraerts T
- 179 Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function
Reeves EP, McCarthy C, McElvaney OJ, Vijayan MSN, White MM, Dunlea DM, Pohl K, Lacey N, McElvaney NG
- 192 Postoperative fluid management
Kayilioglu SI, Dinc T, Sozen I, Bostanoglu A, Cete M, Coskun F
- 202 Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums
Gupta S, Tiruvoipati R, Green C, Botha J, Tran H
- 213 Steps to consider in the approach and management of critically ill patient with spontaneous intracerebral hemorrhage
Godoy DA, Piñero GR, Koller P, Masotti L, Di Napoli M

MINIREVIEWS

- 230 Myeloproliferative and thrombotic burden and treatment outcome of thrombocythemia and polycythemia patients
Michiels JJ
- 240 Intensive care organisation: Should there be a separate intensive care unit for critically injured patients?
Timmers TK, Verhofstad MHJ, Leenen LPH
- 244 Severe scrub typhus infection: Clinical features, diagnostic challenges and management
Peter JV, Sudarsan TI, Prakash JAJ, Varghese GM

ORIGINAL ARTICLE**Clinical Trials Study**

- 251 Landiolol, an ultra-short-acting β 1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis

Okajima M, Takamura M, Taniguchi T

Observational Study

- 258 Outcomes of critically ill cancer patients with *Acinetobacter baumannii* infection

Ñamendys-Silva SA, Correa-García P, García-Guillén FJ, González-Herrera MO, Pérez-Alonso A, Texcocano-Becerra J, Herrera-Gómez A, Cornejo-Juárez P, Meneses-García A

Contents

World Journal of Critical Care Medicine
Volume 4 Number 3 August 4, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Juan Antonio Llompart-Pou, MD, PhD, Intensive Care Unit, Hospital Universitari Son Espases, Carretera Valldemossa, 79 Palma de Mallorca, 07010, Spain

AIM AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, and application of bronchofiberscopy in critically ill patients.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Critical Care Medicine is now indexed in PubMed Central, PubMed, Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Huan-Liang Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Yaseen Mohamed Arabi, MD, FCCP, FCCM, Associate Professor, Chairman, Intensive Care Department, King Saud Bin Abdulaziz University, Medical Director, Respiratory Services, King Abdulaziz Medical City, National Guard Hospital, Riyadh, PO Box 22490, Riyadh 11426, Saudi Arabia

Derek S Wheeler, MD, FAAP, FCCP, FCCM, Associate Professor, Associate Patient Safety Officer, Medical Director, Pediatric Intensive Care Unit, Division of Critical Care Medicine, James M. Anderson Center for Health Systems Excellence, The Center for Simulation and Research, Co-Director, The Center

for Acute Care Nephrology, Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>

<http://www.wjnet.com>

PUBLICATION DATE

August 4, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

From bronchiolitis guideline to practice: A critical care perspective

James A Lin, Andranik Madikians

James A Lin, Andranik Madikians, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Mattel Children's Hospital UCLA, University of California, Los Angeles, CA 90095, United States

Author contributions: Both authors contributed to this manuscript.

Conflict-of-interest statement: The authors have disclosed that they have no potential conflicts of interest (including but not limited to commercial, personal, political, intellectual, or religious interests) that are related to the work submitted for consideration of publication. This is an unfunded work.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: James A Lin, MD, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Mattel Children's Hospital UCLA, 10833 Le Conte Ave, Mail Code 175217, Los Angeles, CA 90095, United States. jameslin@mednet.ucla.edu
Telephone: +1-310-8259124
Fax: +1-310-7946623

Received: March 5, 2015
Peer-review started: March 5, 2015
First decision: April 27, 2015
Revised: June 12, 2015
Accepted: July 11, 2015
Article in press: July 14, 2015
Published online: August 4, 2015

Abstract

Acute viral bronchiolitis is a leading cause of admission

to pediatric intensive care units, but research on the care of these critically ill infants has been limited. Pathology of viral bronchiolitis revealed respiratory obstruction due to intraluminal debris and edema of the airways and vasculature. This and clinical evidence suggest that airway clearance interventions such as hypertonic saline nebulizers and pulmonary toilet devices may be of benefit, particularly in situations of atelectasis associated with bronchiolitis. Research to distinguish an underlying asthma predisposition in wheezing infants with viral bronchiolitis may one day lead to guidance on when to trial bronchodilator therapy. Considering the paucity of critical care research in pediatric viral bronchiolitis, intensive care practitioners must substantially rely on individualization of therapies based on bedside clinical assessments. However, with the introduction of new diagnostic and respiratory technologies, our ability to support critically ill infants with acute viral bronchiolitis will continue to advance.

Key words: Respiratory syncytial virus; Rhinovirus; Asthma; Hypertonic nebulized saline; Acute viral bronchiolitis

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pediatric acute viral bronchiolitis is characterized by small airways obstruction due to inflammatory infiltrates and debris. While this pathology has little or no overlap with asthma, the clinical presentation of wheezing may be similar. Emerging methods to distinguish asthmatics from the general bronchiolitis population, stratify patients according to illness severity, and provide more effective pulmonary clearance and respiratory support may improve outcomes for these patients in the pediatric intensive care unit.

Lin JA, Madikians A. From bronchiolitis guideline to practice: A critical care perspective. *World J Crit Care Med* 2015;

4(3): 152-158 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/152.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.152>

INTRODUCTION AND PURPOSE OF THIS PAPER

Widely recognized as the most common cause of hospitalization for infants, bronchiolitis is responsible for more than 100000 hospitalizations annually and poses a significant risk for respiratory failure requiring mechanical ventilation in infants^[1]. Approximately 5% to 30% of infants hospitalized with bronchiolitis require pediatric intensive care^[2-4]. To address the needs of this patient population, many institutions have established bronchiolitis order sets and pathways. A number of issues now prompt the need to update and reconsider the implementation of bronchiolitis pathways: institution of new electronic medical systems under the Meaningful Use program^[5], the burgeoning pediatric hospitalist movement^[6], a national trend toward protocolized and evidence-based hospital care, and the recent publication of an updated AAP bronchiolitis guideline^[7].

CLINICAL PRESENTATION AND PATHOLOGY

Bronchiolitis is typically recognized clinically by the presence of wheeze, signs and symptoms of upper and lower respiratory tract infection, and respiratory distress^[7]. Apnea can be a major finding, especially in younger infants^[8]. Pathological studies of fatal RSV bronchiolitis have revealed multiple contributing factors to obstruction of small to large-sized airways: intraluminal debris, airway wall edema, and compression by edematous bronchial arteries and inflammatory peri-bronchial lymphoid follicular aggregates (Figure 1). The intraluminal debris may be composed of mucus, fibrin, epithelial cells, and inflammatory cells^[9].

MICROBIOLOGY

Etiologic agents of bronchiolitis include most prominently respiratory syncytial virus (RSV) and rhinovirus^[7]. Additional viruses implicated in acute bronchiolitis include parainfluenza virus, influenza virus, human metapneumovirus, bocavirus, adenovirus, and coronavirus^[7,10].

What is the significance of viral identification in acute bronchiolitis? The triple mission of academic health centers is to deliver leading-edge patient care, conduct research, and educate. In the United States, more than 500 clinical laboratories, many of which are maintained by academic centers, participate in the National Respiratory and Enteric Virus Surveillance System (NREVSS). The Centers for Disease Control

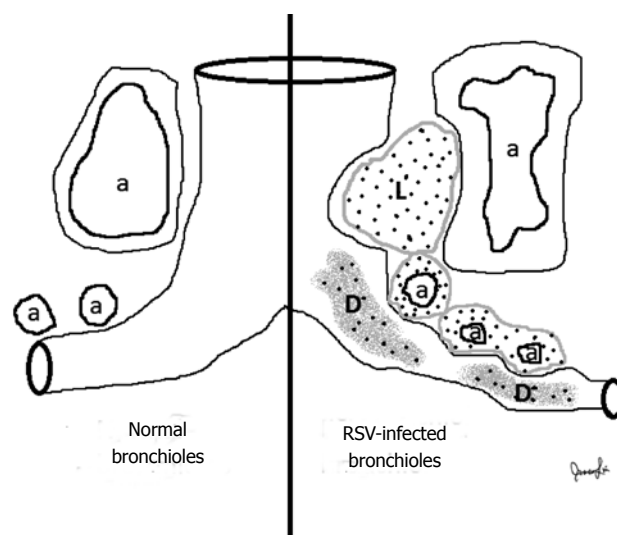


Figure 1 Respiratory syncytial virus infection is associated with vasocentric inflammation affecting bronchioles. Lymphoid aggregates (L), probably developing from bronchiolar-associated lymphoid tissue, are found between pulmonary arteries/arterioles (a) and bronchioles. Congested arterioles surrounding bronchioles contribute to airways obstruction, along with intraluminal debris (D) consisting of mucus, fibrin, epithelial cells, and inflammatory cells. While neutrophils are occasionally obtained from bronchoalveolar lavage, macrophages are the predominant inflammatory cell type in the submucosal infiltrates and intraluminal locations.

and Prevention (CDC) relies on NREVSS to monitor temporal and geographic patterns of relevant virus infections. These viruses significantly include RSV, human metapneumovirus, respiratory adenovirus, and human parainfluenza virus. This surveillance system constitutes an important part of the CDC's efforts to prevent and control respiratory and enteric viral diseases. For instance, an outbreak of enterovirus D68 in 2014 was identified in the Midwestern United States and subsequently spread throughout the United States. Enterovirus D68 caused unusually severe respiratory illnesses, with almost all confirmed cases confined to children. Although the disease was not reportable nationally, "laboratory detections of enterovirus... are reported voluntarily to (NREVSS).... (Suspected) clusters or outbreaks should be reported to local or state health department"^[11]. Identifying viruses that cause illnesses resembling asthma exacerbations is important for the overall scientific goal of understanding respiratory diseases in general. This leads to the philosophic question of whether microbiological investigation of bronchiolitis-causing viruses at centers participating in NREVSS should be regarded differently from nonparticipating centers. Viral identification is an important part of an academic institution's broader societal, educational, and research mission. Additionally, for the patient's family, knowledge that their hospitalized child has RSV or non-RSV virus infection may provide important prognostic information in terms of well-studied risk factors for mortality associated with RSV, potential for longer hospitalization with RSV vs rhinovirus^[7], reduced likelihood of bacterial infection

Table 1 Respiratory syncytial virus reinfection risk

Ref.	Year	n	Reinfection risk
Henderson <i>et al</i> ^[39]	1979	78	74% by age 2 if infected in 1 st year of age
Glezen <i>et al</i> ^[40]	1986	125	76% by 24 mo age if infected before 12 mo age
Hall <i>et al</i> ^[15]	1991	15	50% at first challenge with RSV 2 mo after initial infection
Kawasaki <i>et al</i> ^[16]	2004	165	25% within a year of first RSV infection

n: Total cohort of subjects studied; RSV: Respiratory syncytial virus.

in non-critically ill patients with community-acquired pneumonia^[12], and potentially increased risk of asthma associated with rhinovirus^[13,14]. Finally, a virology-positive diagnosis of RSV or another well-established bronchiolitis-causing agent would possibly help to distinguish cases of bronchiolitis from asthmatics with first-time acute wheeze, although this issue remains under investigation (see section on Asthma below).

What is the risk of RSV reinfection? The most recent AAP guidelines suggest that RSV prophylaxis may be discontinued after breakthrough RSV infection^[7]. We conducted a literature search to clarify the reinfection risk of RSV in infants receiving palivizumab prophylaxis who experience an acute episode of bronchiolitis. Previous literature has demonstrated that RSV infection is highly prevalent and only partially limited by acquired immunity (Table 1). Risk of reinfection may be related to serum titers of RSV-specific antibody^[15,16]. These data suggest that the reinfection risk for RSV in the absence of ongoing passive immunization is high, is correlated with diminished serum titers of RSV-neutralizing antibodies, and can occur within the same RSV season. To our knowledge, neither the effective development of adaptive host immunity to RSV infection in the setting of passive immunization, nor the incidence of RSV reinfection after palivizumab withdrawal has been reported.

SCORING SYSTEM

A scoring system for bronchiolitis would help to standardize care and potentially improve outcomes. Unfortunately, no clinical scoring system has been appropriately validated for reliability, physiologic correlation, and clinical course^[17]. The original basis of bronchiolitis scores was physical examination of respiratory distress using commonly assessed clinical variables^[18]. Over time, continuing reassessment of bronchiolitis scoring has made apparent that the most common scoring system for bronchiolitis, the RDAI, has poor construct validity for overall respiratory status and limited discriminative ability to determine major clinical outcomes like length of stay^[19]. Recent efforts have focused on modeling clinical indicators associated with worse clinical outcomes. A secondary analysis of a randomized, controlled multicenter trial in 20 emergency departments related to bronchiolitis

concluded that oxygen saturation was the best predictor of hospitalization and length of stay^[20]. Among previously healthy infants with RSV bronchiolitis who were admitted to a single academic center, risk factors for respiratory failure that were identified in the emergency department included lethargy, grunting, and PaCO₂ ≥ 65 mmHg^[4]. Prodhan and colleagues also noted that among RSV-infected infants admitted to the intensive care unit with respiratory failure, the major radiologic predictor of prolonged mechanical ventilation was atelectasis, not hyperinflation^[21]. Walsh *et al*^[22] validated a model to predict admission from the emergency department based on age, dehydration, work of breathing, and initial heart rate. Weisgerber *et al*^[23] developed a model to predict prolonged length of stay based on need for supplemental oxygen, respiratory rate, gestation, and caloric intake. The topic of predictive modeling for bronchiolitis has recently been reviewed systematically^[24]. Development of a clinical score for bronchiolitis that accurately reflects relevant indicators of bronchiolitis outcomes could potentially enable research on earlier interventions to ameliorate or prevent critical bronchiolitis disease.

ASTHMA EVALUATION IN EARLY CHILDHOOD

The key differential diagnosis when evaluating a wheezing infant with viral respiratory disease is asthma exacerbation. Viral respiratory infections - especially RSV, parainfluenza, and rhinovirus - are identified by the Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma to be "one of the most important causes of asthma exacerbation and may also contribute to the development of asthma"^[25]. Approximately 40% of infants hospitalized with RSV may continue to wheeze or have asthma even into young adulthood^[26]. Importantly, children who develop asthma symptoms before the age of 3 years are more likely to experience declines in lung function growth than those who develop asthma symptoms after 3 years of age^[25]. Thus, efforts to predict development of childhood asthma are ongoing. While a thorough review of asthma prediction is beyond the scope of this editorial, we present as examples 3 asthma prediction tools in Table 2^[27-29]. The wide range of predictive values is notable, which may be attributable to the different age ranges and clinical baseline of the analyzed patient cohorts. As efforts continue to determine whether early anti-inflammatory therapies can alter the decline in lung function growth^[30] associated with early childhood asthma, it seems likely that research will return to focus on wheezing associated with preschool viral illness. The proscription against a bronchodilator trial in the latest AAP bronchiolitis guideline - regardless of history of recurrent wheeze, atopy, or family history of asthma - will need to be reconciled with both asthma biology and more long-term efforts to modify the natural history of

Table 2 Selected asthma prediction tools

Ref.	Clough <i>et al</i> ^[29]	Castro-Rodríguez <i>et al</i> ^[27]	Zhang <i>et al</i> ^[28]
Year	1999	2000	2014
<i>n</i>	107	1246	128
Cohort	Age 3 mo to 3 yr Wheeze onset < 12 wk prior Parental history of asthma or eczema Parental positive allergen skin prick test	Longitudinal healthy birth cohort	Age 2-20 mo 1 st wheeze
Outcome prediction	Ongoing wheeze requiring treatment 1 yr after presentation	Active asthma during the school years 6-13	Multi-trigger wheezing after 2 yr
Prediction results	71% accuracy overall, 57% sensitivity, 84% specificity, 76% PPV, 68% NPV	42% sensitivity, 85% specificity, 59% PPV, 73% NPV	95% sensitivity, 74% specificity, 59% PPV, 94% NPV
Components of tool	Age at presentation Serum soluble interleukin-2 receptor concentration	Wheezing by parent report Major criteria: parental MD asthma, MD eczema Minor criteria: MD allergic rhinitis, Wheezing apart from colds, eosinophilia ≥ 4%	Wheezing severity score Family or personal history of atopic disease Number of exfoliated airway epithelial cells in sputum

n: Number of subjects; NPV: Negative predictive value; PPV: Positive predictive value; ROC: Receiver operator characteristic.

childhood asthma.

BETA2-AGONISTS FOR ACUTE PEDIATRIC BRONCHIOLITIS

The relevant Cochrane review for bronchodilator therapy in bronchiolitis is directed at first-time wheezing infants receiving beta2-agonists. Exclusion criteria for studies on first-time wheezing infants generally included prior history of wheeze, previous bronchodilator or steroid use, and underlying lung or cardiac disease (including asthma). Additionally, most of the studies excluded patients requiring intensive care. Regarding bronchodilators, the AAP bronchiolitis guideline noted "variable study designs" and "inclusion of infants who had a history of previous wheezing in some studies". This is an unreferenced statement and requires clarification. Of the 33 studies included in the most recent relevant Cochrane analysis, only 4 studies included infants with prior history of wheeze. Two of those studies included only 3 or fewer infants with prior wheeze in each study arm^[17]. In other words, the inclusion of infants with any prior wheeze in bronchodilator trials for bronchiolitis was extremely limited. The AAP guideline makes reference to this: "Those studies showing benefit (of bronchodilators)... include older children with recurrent wheezing.... Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction..., attempts to define a subgroup of responders have not been successful to date". Furthermore, the AAP guideline goes on to state, "Children with severe disease or with respiratory failure were generally excluded from these trials, and this evidence cannot be generalized to these situations"^[7]. Therefore, significant question remains as to whether to trial a beta2-agonist in infants with prior history of wheezing, atopy, or more severe clinical presentations of acute viral bronchiolitis.

CHEST RADIOGRAPHY, ATELECTASIS AND AIRWAY CLEARANCE THERAPY

The AAP bronchiolitis guideline recommends against routine chest radiography in children with bronchiolitis, except for "cases in which respiratory effort is severe enough to warrant ICU admission or where signs of an airway complication (such as pneumothorax) are present"^[7].

While mild-to-moderate presentations of bronchiolitis are unlikely to benefit from chest radiography, detection of radiographic atelectasis in more severe disease may be clinically important. In a study of 46 children with RSV-related respiratory failure, a multiple logistic regression model was developed by Prodhon *et al*^[4,21] to predict length of mechanical ventilation. After excluding hyperinflation due to lack of association, the model included only age and radiologic atelectasis. On days 1 and 2 of mechanical ventilation this model correctly classified patients requiring > 8 d of mechanical ventilation in 84% of cases, and had an area under the ROC curve of 0.92^[21]. This suggests that development of atelectasis in severe bronchiolitis is highly correlated with worse clinical outcome.

The cumulative literature on severe bronchiolitis and our own clinical experience in pediatric intensive care support the idea that the ability to clear obstructed airways and prevent or reverse atelectasis is directly related to an improved clinical course. That atelectasis predicts clinical outcome substantially explains why the literature on chest physiotherapy in acute bronchiolitis in infants has been uniformly negative. As reported in the relevant Cochrane review^[31], patient selection for these trials did not specifically test whether patients with evidence of impaired mucus clearance would fare better with chest physiotherapy. Atelectasis, when reported at all, was in the range of 10%-25% of subjects. In one of the trials, a patient in the control

arm who developed atelectasis was withdrawn from the study in order to receive chest physiotherapy^[32]. This suggests that randomized trials of chest physiotherapy may be limited by clinicians who would not allow their patients to participate if the patients were clinically likely to benefit from chest physiotherapy. Most of the chest physiotherapy trials were conducted on small numbers of subjects. The data could not be pooled because of major differences between studies in both study design and chest physiotherapy technique. To our knowledge, none of the chest physiotherapy trials in bronchiolitis tested recent pulmonary toilet devices like The Vest (pneumovest), intrapulmonary percussive ventilator, MetaNeb, or Cough Assist. A randomized trial on the use of cough assist in acute bronchiolitis is currently underway.

Currently the literature on chest physiotherapy in acute bronchiolitis should be regarded as limited to non-critically ill bronchiolitis and inadequate to make any conclusions regarding patients with suspected or radiologic atelectasis. We believe that clinicians should make individualized decisions on chest radiography and chest physiotherapy in bronchiolitis, particularly to evaluate and treat atelectasis. Although this may seem to be in contrast to the AAP guideline: "Clinicians should not use chest physiotherapy for infants and children with a diagnosis of bronchiolitis"^[7], the nature of the guidelines is as "an evidence-based shared baseline.... (not to) tell you what to do in the case of every patient"^[33].

THREE PERCENT OF HYPERTONIC SALINE NEBULIZER THERAPY

Nebulized hypertonic saline potentially addresses the pathophysiology of airways obstruction in acute viral bronchiolitis by reducing pulmonary edema and loosening intraluminal debris to facilitate mobilization. The most recent Cochrane review on hypertonic saline therapy for acute bronchiolitis was undertaken on 11 inpatient and outpatient studies, all of which were randomized, double-blind, parallel-group, controlled trials (RCTs) using 0.9% saline as a control. All of the trials excluded patients with prior wheeze or severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation < 85% on room air). The concentration of hypertonic saline was 3% in all but one trial, which included both 3% and 5% concentrations. The 6 inpatient trials involving 500 participants revealed a pooled reduction in length of hospital stay by 1.15 d (95%CI: -1.49 to -0.82, $P < 0.0001$) for children treated with hypertonic saline, with average stays ranging 3.5 to 7.4 d. All 6 inpatient trials demonstrated a benefit in reducing duration of hospitalization^[34]. Subsequent to this Cochrane review, randomized trials of inhaled hypertonic saline have revealed mixed results^[35-38]. Resolving the differences between the many RCTs on nebulized hypertonic saline

will likely require either a meta-analysis approach or an updated Cochrane review. In the meantime, evidence in support of 3% hypertonic saline therapy for hospitalized pediatric bronchiolitis includes clinical and biologic plausibility, numerous well-designed RCT's, substantial benefit in a number of trials, and virtually no observed harm, including a notable absence of bronchospasm^[34]. While the AAP guideline on hypertonic saline nebulizer for inpatient bronchiolitis appropriately balances the mostly if not uniformly positive evidence, the development of an institutional protocol could reasonably implement hypertonic saline for every admitted patient with acute bronchiolitis, especially if the institutional average length of stay for bronchiolitis exceeds three days.

ADDRESSING THE ACADEMIC MISSION OF ADVANCING HEALTH CARE

In conclusion, we applaud the 2014 revision of the AAP guideline on bronchiolitis and suggest further research to: (1) develop and validate severity scores to help guide clinical therapies; (2) incorporate early identification of childhood asthma; (3) study methods to identify and address atelectasis; and (4) consolidate the available data on inhaled hypertonic saline. Most importantly for the bedside practitioner, the pragmatic clinical setting and individualized assessment continue to guide medical care. With the development of new medical technologies and informatics, we are beginning to investigate bronchiolitis using a different set of tools and in a different way from those in the past, although constrained by the same limitations on resources and funds. In this way, academic centers can continue to fulfill our mission to educate, study, and provide the best health care to each of our patients.

REFERENCES

- 1 **Hasegawa K**, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics* 2013; **132**: 28-36 [PMID: 23733801 DOI: 10.1542/peds.2012-3877]
- 2 **Papenburg J**, Hamelin MÈ, Ouhoumane N, Carboneau J, Ouakki M, Raymond F, Robitaille L, Corbeil J, Caouette G, Frenette L, De Serres G, Boivin G. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. *J Infect Dis* 2012; **206**: 178-189 [PMID: 22551815 DOI: 10.1093/infdis/jis333]
- 3 **Prais D**, Schonfeld T, Amir J. Admission to the intensive care unit for respiratory syncytial virus bronchiolitis: a national survey before palivizumab use. *Pediatrics* 2003; **112**: 548-552 [PMID: 12949282 DOI: 10.1542/peds.112.3.548]
- 4 **Prodhan P**, Sharoor-Karni S, Lin J, Noviski N. Predictors of respiratory failure among previously healthy children with respiratory syncytial virus infection. *Am J Emerg Med* 2011; **29**: 168-173 [PMID: 20825782 DOI: 10.1016/j.ajem.2009.08.020]
- 5 **Blumenthal D**, Tavenner M. The "meaningful use" regulation for electronic health records. *N Engl J Med* 2010; **363**: 501-504 [PMID: 20647183 DOI: 10.1056/NEJMp1006114]
- 6 **Mussman GM**, Conway PH. Pediatric hospitalist systems versus traditional models of care: effect on quality and cost outcomes.

- J Hosp Med* 2012; **7**: 350-357 [PMID: 21972204 DOI: 10.1002/jhm.951]
- 7 **Ralston SL**, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadowski AM, Johnson DW, Light MJ, Maraqa NF, Mendonca EA, Phelan KJ, Zorc JJ, Stanko-Lopp D, Brown MA, Nathanson I, Rosenblum E, Sayles S, Hernandez-Cancio S. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014; **134**: e1474-e1502 [PMID: 25349312 DOI: 10.1542/peds.2014-2742]
- 8 **Schroeder AR**, Mansbach JM, Stevenson M, Macias CG, Fisher ES, Barcega B, Sullivan AF, Espinola JA, Piedra PA, Camargo CA. Apnea in children hospitalized with bronchiolitis. *Pediatrics* 2013; **132**: e1194-e1201 [PMID: 24101759 DOI: 10.1542/peds.2013-1501]
- 9 **Johnson JE**, Gonzales RA, Olson SJ, Wright PF, Graham BS. The histopathology of fatal untreated human respiratory syncytial virus infection. *Mod Pathol* 2007; **20**: 108-119 [PMID: 17143259]
- 10 **Everard ML**. Acute bronchiolitis and croup. *Pediatr Clin North Am* 2009; **56**: 119-133, x-xi [PMID: 19135584 DOI: 10.1016/j.pcl.2008.10.007]
- 11 **Midgley CM**, Jackson MA, Selvarangan R, Turabelidze G, Obringer E, Johnson D, Giles BL, Patel A, Echols F, Oberste MS, Nix WA, Watson JT, Gerber SI. Severe respiratory illness associated with enterovirus D68 - Missouri and Illinois, 2014. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 798-799 [PMID: 25211545]
- 12 **Bradley JS**, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH, Moore MR, St Peter SD, Stockwell JA, Swanson JT. Executive summary: the management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; **53**: 617-630 [PMID: 21890766 DOI: 10.1093/cid/cir625]
- 13 **Calışkan M**, Bochkov YA, Kreiner-Møller E, Bønnelykke K, Stein MM, Du G, Bisgaard H, Jackson DJ, Gern JE, Lemanske RF, Nicolae DL, Ober C. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013; **368**: 1398-1407 [PMID: 23534543 DOI: 10.1056/NEJMoa1211592]
- 14 **Kotaniemi-Syrjänen A**, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy-the first sign of childhood asthma? *J Allergy Clin Immunol* 2003; **111**: 66-71 [PMID: 12532098 DOI: 10.1067/mai.2003.33]
- 15 **Hall CB**, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. *J Infect Dis* 1991; **163**: 693-698 [PMID: 2010624 DOI: 10.1093/infdis/163.4.693]
- 16 **Kawasaki Y**, Hosoya M, Katayose M, Suzuki H. Role of serum neutralizing antibody in reinfection of respiratory syncytial virus. *Pediatr Int* 2004; **46**: 126-129 [PMID: 15056236 DOI: 10.1046/j.1442-200x.2004.01860.x]
- 17 **Gadowski AM**, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 2014; **6**: CD001266 [PMID: 24937099 DOI: 10.1002/14651858.CD001266.pub4]
- 18 **Lowell DI**, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics* 1987; **79**: 939-945 [PMID: 3295741]
- 19 **Destino L**, Weisgerber MC, Soung P, Bakalinski D, Yan K, Rehborg R, Wagner DR, Gorelick MH, Simpson P. Validity of respiratory scores in bronchiolitis. *Hosp Pediatr* 2012; **2**: 202-209 [PMID: 24313026 DOI: 10.1542/hpeds.2012-0013]
- 20 **Corneli HM**, Zorc JJ, Holubkov R, Bregstein JS, Brown KM, Mahajan P, Kuppermann N. Bronchiolitis: clinical characteristics associated with hospitalization and length of stay. *Pediatr Emerg Care* 2012; **28**: 99-103 [PMID: 22270499 DOI: 10.1097/PEC.0b013e3182440b9b]
- 21 **Prodhan P**, Westra SJ, Lin J, Karni-Sharoor S, Regan S, Noviski N. Chest radiological patterns predict the duration of mechanical ventilation in children with RSV infection. *Pediatr Radiol* 2009; **39**: 117-123 [PMID: 19005648 DOI: 10.1007/s00247-008-1042-3]
- 22 **Walsh P**, Rothenberg SJ, O'Doherty S, Hoey H, Healy R. A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis. *Eur J Emerg Med* 2004; **11**: 265-272 [PMID: 15359199 DOI: 10.1097/00063110-200410000-00005]
- 23 **Weisgerber MC**, Lye PS, Li SH, Bakalinski D, Gedeit R, Simpson P, Gorelick MH. Factors predicting prolonged hospital stay for infants with bronchiolitis. *J Hosp Med* 2011; **6**: 264-270 [PMID: 21661099 DOI: 10.1002/jhm.903]
- 24 **Luo G**, Nkoy FL, Gesteland PH, Glasgow TS, Stone BL. A systematic review of predictive modeling for bronchiolitis. *Int J Med Inform* 2014; **83**: 691-714 [PMID: 25106933 DOI: 10.1016/j.ijmedinf.2014.07.005]
- 25 **National Asthma Education and Prevention Program**. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma: Full Report 2007, in National Asthma Education and Prevention Program 2007, National Institutes of Health: National Heart Lung and Blood Institute: Bethesda, 2007: 415
- 26 **Sigurs N**, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010; **65**: 1045-1052 [PMID: 20581410 DOI: 10.1136/thx.2009.121582]
- 27 **Castro-Rodríguez JA**, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; **162**: 1403-1406 [PMID: 11029352 DOI: 10.1164/ajrccm.162.4.9912111]
- 28 **Zhang Y**, Zhou C, Liu J, Yang H, Zhao S. A new index to identify risk of multi-trigger wheezing in infants with first episode of wheezing. *J Asthma* 2014; **51**: 1043-1048 [PMID: 24986248 DOI: 10.3109/02770903.2014.936449]
- 29 **Clough JB**, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999; **160**: 1473-1480 [PMID: 10556108 DOI: 10.1164/ajrccm.160.5.9807019]
- 30 **Grol MH**, Gerritsen J, Vonk JM, Schouten JP, Koëter GH, Rijcken B, Postma DS. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. A 30-year follow-up study. *Am J Respir Crit Care Med* 1999; **160**: 1830-1837 [PMID: 10588593 DOI: 10.1164/ajrccm.160.6.9812100]
- 31 **Roqué i Figuls M**, Giné-Garriga M, Granados Rugeles C, Perrotta C. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev* 2012; **2**: CD004873 [PMID: 22336805 DOI: 10.1002/14651858.CD004873.pub4]
- 32 **Bohé L**, Ferrero ME, Cuestas E, Polliotto L, Genoff M. Indications of conventional chest physiotherapy in acute bronchiolitis. *Medicina (B Aires)* 2004; **64**: 198-200 [PMID: 15239532]
- 33 **Quinonez RA**, Ralston SL. Bronchiolitis: the rationale behind the new AAP guideline. *Medscape* 2014, WebMD LLC: New York, NY, 2014. Available from: URL: http://www.medscape.com/viewarticle/834677_5
- 34 **Zhang L**, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev* 2013; **7**: CD006458 [PMID: 23900970 DOI: 10.1002/14651858.CD006458.pub3]
- 35 **Everard ML**, Hind D, Ugonna K, Freeman J, Bradburn M, Cooper CL, Cross E, Maguire C, Cantrill H, Alexander J, McNamara PS. SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax* 2014; **69**: 1105-1112 [PMID: 25389139 DOI: 10.1136/thoraxjnl-2014-205953]
- 36 **Wu S**, Baker C, Lang ME, Schrager SM, Liley FF, Papa C, Mira V, Balkian A, Mason WH. Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial. *JAMA Pediatr* 2014; **168**: 657-663 [PMID: 24862623 DOI: 10.1001/jamapediatrics.2014.301]
- 37 **Florin TA**, Shaw KN, Kittick M, Yakscoe S, Zorc JJ. Nebulized hypertonic saline for bronchiolitis in the emergency department: a randomized clinical trial. *JAMA Pediatr* 2014; **168**: 664-670 [PMID: 24862342 DOI: 10.1001/jamapediatrics.2013.5306]
- 38 **Sharma BS**, Gupta MK, Rafik SP. Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: a randomized

- controlled trial. *Indian Pediatr* 2013; **50**: 743-747 [PMID: 23502662 DOI: 10.1007/s13312-013-0216-8]
- 39 **Henderson FW**, Collier AM, Clyde WA, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N Engl J Med* 1979; **300**: 530-534 [PMID: 763253 DOI: 10.1056/NEJM197903083001004]
- 40 **Glezen WP**, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986; **140**: 543-546 [PMID: 3706232 DOI: 10.1001/archpedi.1986.02140200053026]
- P- Reviewer:** Belliato M, Kelesidis T, Zhang YJ **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL



Opening the doors of the intensive care unit to cancer patients: A current perspective

Silvio A Ñamendys-Silva, Erika P Plata-Menchaca, Eduardo Rivero-Sigarroa, Angel Herrera-Gómez

Silvio A Ñamendys-Silva, Erika P Plata-Menchaca, Eduardo Rivero-Sigarroa, Department of Critical Care Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City 14000, Mexico

Silvio A Ñamendys-Silva, Angel Herrera-Gómez, Department of Critical Care Medicine, Instituto Nacional de Cancerología, México City 14080, Mexico

Author contributions: Ñamendys-Silva SA designed research, analyzed and wrote the paper; Plata-Menchaca EP contributed new reagents or analytic tools and wrote the paper; Rivero-Sigarroa E and Herrera-Gómez A analyzed the data; all authors read and approved the final paper.

Conflict-of-interest statement: None of the authors have commercial association or financial involvement that might pose a conflict of interest in connection with this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Silvio A Ñamendys-Silva, MD, MSc, FCCP, Department of Critical Care Medicine, Instituto Nacional de Cancerología, México. Av. San Fernando No. 22, Col. Sección XVI, Delegación Tlalpan, México City 14080, Mexico. snamendys@incan.edu.mx
Telephone: +52-55-47471020
Fax: +52-55-734664

Received: March 23, 2015
Peer-review started: March 25, 2015
First decision: June 3, 2015
Revised: June 12, 2015
Accepted: July 16, 2015
Article in press: July 17, 2015
Published online: August 4, 2015

Abstract

The introduction of new treatments for cancer and advances in the intensive care of critically ill cancer patients has improved the prognosis and survival. In recent years, the classical intensive care unit (ICU) admission comorbidity criteria used for this group of patients have been discouraged since the risk factors for death that have been studied, mainly the number and severity of organic failures, allow us to understand the determinants of the prognosis inside the ICU. However, the availability of intensive care resources is dissimilar by country, and these differences are known to alter the indications for admission to critical care setting. Three to five days of ICU management is warranted before making a final decision (ICU trial) to consider keep down intensive management of critically ill cancer patients. Nowadays, taking into account only the diagnosis of cancer to consider ICU admission of patients who need full-supporting management is no longer justified.

Key words: Intensive care unit; Critical care setting; Cancer patients; Critically ill cancer patients; Organ failures

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The number and severity of organ failures are still the most important determinants for in-hospital mortality of critically ill cancer patients. Thus, an early intensive care unit admission is crucial to impact in the short-term prognosis of this population.

Ñamendys-Silva SA, Plata-Menchaca EP, Rivero-Sigarroa E, Herrera-Gómez A. Opening the doors of the intensive care unit to cancer patients: A current perspective. *World J Crit Care Med* 2015; 4(3): 159-162 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/159.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.159>

INTRODUCTION

The concept of futility was used to support either refuse of intensive care unit (ICU) admission or early treatment withdrawal decisions for critically ill cancer patients. Nevertheless, emerging of new treatments for cancer and recent advances in intensive care medicine has improved prognosis and survival.

At present, the classical comorbidity criteria used for ICU admission in this group of patients have been discouraged since the risk factors for death that have been studied, mainly the number and severity of organ failures, allow us to understand the determinants of the outcomes inside the ICU. In our center, the overall mortality was 17.5% over a four-year period, provided an appropriate selection of patients, an adequate evaluation of predictors of ICU mortality and treatment outcomes are necessary in each case evaluation^[1-5].

Also, the clinician should be updated in the recent information available about prognostic factors that contribute to in-hospital mortality of critically ill patients with cancer. Furthermore, the availability of intensive care resources is dissimilar by country, and these differences are known to alter the indications for admission to critical care setting^[6]. Unlike the United States and Canada, Mexico seems to have approximately 1984 ICU beds with mechanical ventilators (1.76 ICU beds per population of 100000)^[7].

Also, clinicians should be hard-headed during discussions and respect the patient's will to choice an invasive treatment. We should take into account the number and severity of organ failures when evaluating patients for ICU admission, beyond the diagnosis of cancer. For this purpose Sequential Organ Failure Assessment (SOFA) or, recently, the Mexican sequential organ failure assessment are useful to evaluate number and severity of organ failures as the main prognostic factor in critically ill patients with cancer. Thus, early admission to the ICU with the lowest possible number of organ failures is recommended^[8-10].

In a substudy of the Sepsis Occurrence in Acutely Ill Patients study, a large prospective cohort that included 198 participating ICUs from 24 European countries, the primary endpoint was death or hospital discharge at 60 d. In this study, Taccone *et al.*^[11] found that ICU and hospital mortality rates were similar in patients with solid tumors and those without cancer.

Aygenel *et al.*^[12] recently described a median of the SOFA score of 9 as a major contributor to mortality of critically ill cancer patients with solid tumors and a median of SOFA score of 10 in patients with hematologic malignancies. Other significant predictors for ICU mortality in patients with solid tumors were lactate dehydrogenase level on admission, sepsis or septic shock during ICU stay, and remission of the underlying cancer. In 2010, Namendys-Silva *et al.*^[2] described that Acute Physiology and Chronic Health Evaluation II score and vasopressor requirement during ICU stay, were independent predictors for ICU mortality in patients

with solid malignancies. Aygenel *et al.*^[12] also found these risk factors to be significant. In general, classic predictors of mortality are no longer relevant, and we should evaluate other characteristics of the cancer patient to decide the admission to the ICU^[2,12].

In addition, age influences minimally on 6-mo survival of critically ill cancer patients^[13], whereas performance status and comorbidity are much more important^[13-15].

In 2013, we made recommendations and developed a management algorithm to guide ICU admission of cancer patients (Table 1)^[16]. In fact, we highlight that this algorithm should not be different from admission criteria of other patients admitted to the ICU without cancer.

There is a subgroup of patients that should not be considered for admission, including those patients with a poor status performance or those who refuse to ICU admission to receive invasive treatment.

Three to five days of ICU management is warranted before making a final decision (ICU trial) to consider keep down intensive management^[17].

When a doubt exists about the criteria for ICU admission, a trial of ICU management should be proposed to assert that no patients are withhold of an opportunity for recovering from their acute condition. When ICU admission is accepted, patients should be treated with a full-supporting management (ICU trial) for at least 3-5 d. By doing this, patients receive everything they need during the first few ICU days and then have their clinical status reassessed after completing this trial. This "full-code status" includes the provision of cancer chemotherapy, antibiotics, and other life-sustaining therapies. After 3 d of full intensive management, an improvement in the number and severity of organ failures indicates that additional life-supporting treatment should be continued; whereas deterioration of clinical status, evaluated by an increase in the number or severity of organ failures, should prompt a discussion of the patients suitable to be still under aggressive treatment^[17].

In addition, patients with tumor lysis syndrome, neoplasm-related pulmonary or renal infiltration, sepsis related to obstructive pneumonia, or ureteral compression may require full-supporting treatment until the cancer chemotherapy becomes effective^[18].

Full ICU treatment should be provided to cancer patients with particular characteristics (Table 1). However, the postoperative care of surgical oncology patients is not always mandatory in the ICU.

In addition, the mortality rate for mechanically ventilated cancer patients remains higher than that for patients with non-malignant diseases^[19,20].

We studied the prognosis and ICU mortality rates for hematologic malignancies patients who required invasive mechanical ventilation (IMV) and for those with solid tumors, being 73% (65/189) and 34.3% (58/169), respectively. Although IMV in cancer patients is still associated with a very high risk of death, the mortality

Table 1 Recommendations for intensive care unit admission of critically ill cancer patients^[16]

Cancer patients who benefit of ICU admission
SOFA score between 7 and 10 or less than 3 organ failures
Recent diagnosis of hemato-oncological disease
Treatment of medical emergencies related to cancer or its treatment; tumor lysis syndrome, pulmonary infiltrates in patients with leukemia or leukostasis as the initial manifestation of leukemia
The likelihood of a cure or probable disease control
Performance status (Eastern Cooperative Oncology Group scale) between 0 and 2
Postoperative intensive care for patients undergoing complex surgical procedures who require hemodynamic monitoring and/or mechanical ventilation

ICU: Intensive care unit.

rate for patients with IMV in our ICU was lower than previously reported^[21-26]. Soares *et al.*^[25] studied prospectively 463 cancer patients on mechanical ventilation. Age > 70 years, severity of acute organ failures, poor performance status, cancer status, and older age were the main determinants of mortality.

In a large multicenter study of 1004 patients with solid or hematological malignancies and acute respiratory distress syndrome (ARDS) meeting the new operational Berlin definition, about 90% of ARDS cases were due to infections. Opportunistic organisms accounted for over one-third of all ARDS cases, with invasive aspergillosis and *Pneumocystis jiroveci* pneumonia in primary ARDS and candidemia in secondary ARDS. The authors concluded that mortality decreased significantly over time to 52%, despite adjustment for patients' ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. This highlights the relevance of optimal patient triage to ICU admission and ARDS management in ICUs that are highly experienced in managing patients with ARDS and malignancies^[27].

There are some interventions well studied in non-cancer patients that could be beneficial in the critical care setting of patients with malignancies. de Almeida *et al.*^[28] recently found that a restrictive transfusion strategy in surgical oncology patients results in more postoperative complications compared with liberal strategy (hemoglobin trigger of 9 g/dL). The absolute risk reduction for the liberal strategy was 16% (95%CI: 3.8-28.2) and a number needed to treat of 6.2 (95%CI: 3.5-26.5) to avoid postsurgical complications.

Some studies have demonstrated the feasibility of administering chemotherapy in the ICU setting, with admissible short and long-term outcomes, as recently shown by Wohlfarth *et al.*^[29].

CONCLUSION

In conclusion, hesitancy to admit cancer patients to the ICU for advance life supporting therapy is no longer justified if this decision is made based only on the presence of cancer. The clinical oncologist, hematologist and surgical oncologist should be trained with clinical capabilities that will impact in short term outcomes of patients, not only requesting admission to the ICU when they already have vasopressor requirements,

mechanical ventilation, multiple organ failures or palliative care is the only treatment option. Moreover, we should take into account that critically ill cancer patients should be evaluated likewise every other patient before admission to the ICU.

Our aim is to emphasize the clinical relevance of implementing preventive measures to avoid in-hospital death of cancer patients, identifying them at an earlier stage of organ failures, when offering full support to those patients who selectively are candidates to ICU admission will impact on their final outcome.

REFERENCES

1. Namendys-Silva SA, González-Herrera MO, Herrera-Gómez A. Mortality of patients with cancer admitted to intensive care unit. *Am J Hosp Palliat Care* 2013; **30**: 214-215 [PMID: 22556284 DOI: 10.1177/1049909112444157]
2. Namendys-Silva SA, Texcocano-Becerra J, Herrera-Gómez A. Prognostic factors in critically ill patients with solid tumours admitted to an oncological intensive care unit. *Anaesth Intensive Care* 2010; **38**: 317-324 [PMID: 20369766]
3. Darmon M, Azoulay E. Critical care management of cancer patients: cause for optimism and need for objectivity. *Curr Opin Oncol* 2009; **21**: 318-326 [PMID: 19436200 DOI: 10.1097/CCO.0b013e32832b68b6]
4. Mendoza V, Lee A, Marik PE. The hospital-survival and prognostic factors of patients with solid tumors admitted to an ICU. *Am J Hosp Palliat Care* 2008; **25**: 240-243 [PMID: 18539768 DOI: 10.1177/1049909108315523]
5. Pène F, Percheron S, Lemiale V, Viallon V, Claessens YE, Marqué S, Charpentier J, Angus DC, Cariou A, Chiche JD, Mira JP. Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. *Crit Care Med* 2008; **36**: 690-696 [PMID: 18431262 DOI: 10.1097/CCM.0B013E318165314B]
6. Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. *Lancet* 2010; **376**: 1347-1353 [PMID: 20934213 DOI: 10.1016/S0140-6736(10)60143-2]
7. Namendys-Silva SA, García-Guillén FJ, Herrera-Gómez A. Opening the doors of the intensive care unit to patients with hematologic malignancies. *J Clin Oncol* 2014; **32**: 1169-1170 [PMID: 24616316 DOI: 10.1200/JCO.2013.52.1401]
8. Vandijk DM, Depuydt PO, Offner FC, Nallet J, Peleman RA, Steel E, Noens LA, Decruyenaere JM, Benoit DD. Impact of organ dysfunction on mortality in ICU patients with hematologic malignancies. *Intensive Care Med* 2010; **36**: 1744-1750 [PMID: 20480137 DOI: 10.1007/s00134-010-1903-8]
9. Namendys-Silva SA, Silva-Medina MA, Vásquez-Barahona GM, Baltazar-Torres JA, Rivero-Sigarroa E, Fonseca-Lazcano JA, Domínguez-Cherit G. Application of a modified sequential organ failure assessment score to critically ill patients. *Braz J Med Biol Res* 2013; **46**: 186-193 [PMID: 23369978 DOI: 10.1590/1414-431

- X20122308]
- 10 **Namendys-Silva SA**, Texcocano-Becerra J, Herrera-Gómez A. Application of the Sequential Organ Failure Assessment (SOFA) score to patients with cancer admitted to the intensive care unit. *Am J Hosp Palliat Care* 2009; **26**: 341-346 [PMID: 19357377 DOI: 10.1177/1049909109333041]
 - 11 **Taccone FS**, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs. *Crit Care* 2009; **13**: R15 [PMID: 19200368 DOI: 10.1186/cc7713]
 - 12 **Aygenel G**, Turkoglu M, Turkoz Sucak G, Benekli M. Prognostic factors in critically ill cancer patients admitted to the intensive care unit. *J Crit Care* 2014; **29**: 618-626 [PMID: 24612762 DOI: 10.1016/j.jcrc.2014.01.014]
 - 13 **Soares M**, Carvalho MS, Salluh JJ, Ferreira CG, Luiz RR, Rocco JR, Spector N. Effect of age on survival of critically ill patients with cancer. *Crit Care Med* 2006; **34**: 715-721 [PMID: 16521261 DOI: 10.1097/01.ccm.0000201883.05900.3f]
 - 14 **Soares M**, Salluh JJ, Carvalho MS, Darmon M, Rocco JR, Spector N. Prognosis of critically ill patients with cancer and acute renal dysfunction. *J Clin Oncol* 2006; **24**: 4003-4010 [PMID: 16921054 DOI: 10.1200/JCO.2006.05.7869]
 - 15 **Soares M**, Darmon M, Salluh JJ, Ferreira CG, Thiéry G, Schlemmer B, Spector N, Azoulay E. Prognosis of lung cancer patients with life-threatening complications. *Chest* 2007; **131**: 840-846 [PMID: 17356101 DOI: 10.1378/chest.06-2244]
 - 16 **Namendys-Silva SA**, González-Herrera MO, García-Guillén FJ, Texcocano-Becerra J, Herrera-Gómez A. Outcome of critically ill patients with hematological malignancies. *Ann Hematol* 2013; **92**: 699-705 [PMID: 23328791 DOI: 10.1007/s00277-013-1675-7]
 - 17 **Suhag V**, Sunita BS, Sarin A. Intensive Care For Cancer Patients: An Overview. *Asian Austral J Anim* 2014; **13**: 193-201
 - 18 **Thiery G**, Azoulay E, Darmon M, Ciroidi M, De Miranda S, Lévy V, Fieux F, Moreau D, Le Gall JR, Schlemmer B. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. *J Clin Oncol* 2005; **23**: 4406-4413 [PMID: 15994150 DOI: 10.1200/JCO.2005.01.487]
 - 19 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
 - 20 **Esteban A**, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguía C, Nightingale P, Arroliga AC, Tobin MJ. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287**: 345-355 [PMID: 11790214 DOI: 10.1001/jama.287.3.345]
 - 21 **Namendys-Silva SA**, Jarquin-Badiola YD, García-Guillén FJ, Texcocano-Becerra J, Cázares-Mejía R, Herrera-Gómez A. Mechanical ventilation in critically ill cancer patients. *Heart Lung* 2015; **44**: 85-86 [PMID: 25455912 DOI: 10.1016/j.hrtlng.2014.09.004]
 - 22 **Benoit DD**, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Crit Care Med* 2003; **31**: 104-112 [PMID: 12545002]
 - 23 **Depuydt PO**, Benoit DD, Vandewoude KH, Decruyenaere JM, Colardyn FA. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. *Chest* 2004; **126**: 1299-1306 [PMID: 15486396]
 - 24 **Azoulay E**, Thiéry G, Chevret S, Moreau D, Darmon M, Bergeron A, Yang K, Meignin V, Ciroidi M, Le Gall JR, Tazi A, Schlemmer B. The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine* (Baltimore) 2004; **83**: 360-370 [PMID: 15525848]
 - 25 **Soares M**, Salluh JJ, Spector N, Rocco JR. Characteristics and outcomes of cancer patients requiring mechanical ventilatory support for > 24 hrs. *Crit Care Med* 2005; **33**: 520-526 [PMID: 15753742 DOI: 10.1097/01.CCM.0000155783.46747.04]
 - 26 **Azevedo LC**, Caruso P, Silva UV, Torelly AP, Silva E, Rezende E, Netto JJ, Piras C, Lobo SM, Knibel MF, Teles JM, Lima RA, Ferreira BS, Friedman G, Rea-Neto A, Dal-Pizzol F, Bozza FA, Salluh JJ, Soares M. Outcomes for patients with cancer admitted to the ICU requiring ventilatory support: results from a prospective multicenter study. *Chest* 2014; **146**: 257-266 [PMID: 24480886 DOI: 10.1378/chest.13-1870]
 - 27 **Azoulay E**, Lemiale V, Mokart D, Pène F, Kouatchet A, Perez P, Vincent F, Mayaux J, Benoit D, Bruneel F, Meert AP, Nyunga M, Rabbat A, Darmon M. Acute respiratory distress syndrome in patients with malignancies. *Intensive Care Med* 2014; **40**: 1106-1114 [PMID: 24898895 DOI: 10.1007/s00134-014-3354-0]
 - 28 **de Almeida JP**, Vincent JL, Galas FR, de Almeida EP, Fukushima JT, Osawa EA, Bergamin F, Park CL, Nakamura RE, Fonseca SM, Cutait G, Alves JJ, Bazan M, Vieira S, Sandrini AC, Palomba H, Ribeiro U, Crippa A, Dalloglio M, Diz Mdel P, Kalil Filho R, Auler JO, Rhodes A, Hajjar LA. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. *Anesthesiology* 2015; **122**: 29-38 [PMID: 25401417 DOI: 10.1097/ALN.0000000000000511]
 - 29 **Wohlfarth P**, Staudinger T, Sperr WR, Bojic A, Robak O, Hermann A, Laczika K, Carlström A, Riss K, Rabitsch W, Bojic M, Knoebl P, Locker GJ, Obiditsch M, Fuhrmann V, Schellongowski P. Prognostic factors, long-term survival, and outcome of cancer patients receiving chemotherapy in the intensive care unit. *Ann Hematol* 2014; **93**: 1629-1636 [PMID: 24997682 DOI: 10.1007/s00277-014-2141-x]

P- Reviewer: Chen XL, Llompert-Pou J S- Editor: Tian YL

L- Editor: A E- Editor: Wu HL



Brain-lung crosstalk: Implications for neurocritical care patients

Ségolène Mrozek, Jean-Michel Constantin, Thomas Geeraerts

Ségolène Mrozek, Thomas Geeraerts, Anesthesiology and Critical Care Department, Equipe d'accueil "Modélisation de l'agression tissulaire et nociceptive", University Hospital of Toulouse, 31000 Toulouse, France

Jean-Michel Constantin, Department of Anesthesiology and Critical Care Medicine, Estaing Hospital, University Hospital of Clermont-Ferrand, 63000 Clermont-Ferrand, France

Author contributions: Mrozek S, Constantin JM and Geeraerts T contributed equally to this paper.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ségolène Mrozek, MD, Anesthesiology and Critical Care Department, Equipe d'accueil "Modélisation de l'agression tissulaire et nociceptive", University Hospital of Toulouse, University Toulouse 3 Paul Sabatier, 31000 Toulouse, France. mrozek.s@chu-toulouse.fr
Telephone: +33-561-772167
Fax: +33-561-772170

Received: February 8, 2015
Peer-review started: February 9, 2015
First decision: April 10, 2015
Revised: May 8, 2015
Accepted: May 27, 2015
Article in press: May 28, 2015
Published online: August 4, 2015

Abstract

Major pulmonary disorders may occur after brain

injuries as ventilator-associated pneumonia, acute respiratory distress syndrome or neurogenic pulmonary edema. They are key points for the management of brain-injured patients because respiratory failure and mechanical ventilation seem to be a risk factor for increased mortality, poor neurological outcome and longer intensive care unit or hospital length of stay. Brain and lung strongly interact *via* complex pathways from the brain to the lung but also from the lung to the brain. Several hypotheses have been proposed with a particular interest for the recently described "double hit" model. Ventilator setting in brain-injured patients with lung injuries has been poorly studied and intensivists are often fearful to use some parts of protective ventilation in patients with brain injury. This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

Key words: Brain-lung crosstalk; Brain injury; Lung injury; Protective ventilation; Double hit model

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Brain lung crosstalk is a complex interaction from the brain to the lung but also from the lung to the brain. Intensivists are often fearful to use some parts of protective ventilation in patients with brain injuries but if correctly applied, mechanical ventilation could have beneficial effect on brain oxygenation, even if positive end-expiratory pressure and recruitment maneuvers are used. This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

Mrozek S, Constantin JM, Geeraerts T. Brain-lung crosstalk:

Implications for neurocritical care patients. *World J Crit Care Med* 2015; 4(3): 163-178 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/163.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.163>

INTRODUCTION

Brain lung crosstalk is a complex interaction from the brain to the lung but also from the lung to the brain. The occurrence of severe pulmonary injuries after experiencing a brain injury, such as severe traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) or stroke, has been described^[1-5]. These pulmonary injuries include ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary edema (NPE). They are key points for the management of brain-injured patients because respiratory failure and mechanical ventilation seem to be a risk factor for increased mortality, poor neurological outcome and longer intensive care unit (ICU) or hospital length of stay (LOS)^[4-9]. The pathophysiology of brain-lung interaction is complex and several hypotheses have been proposed with a particular interest for the recently described "double hit" model^[1].

This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

LUNG INJURIES AFTER BRAIN INJURIES

Major pulmonary disorders may occur after brain injuries as VAP, ARDS or NPE. In this review, the direct consequences of chest trauma, such as rib fractures, lung contusions or hemo/pneumothorax will not be discussed in the present review. Zygun *et al*^[6], in an observational cohort study, reported non-neurologic organ dysfunctions in 209 patients with severe TBI. Eighty-nine percent of patients had at least one non-neurologic dysfunction (organ system component score ≥ 1), and 81% of patients developed respiratory dysfunction [arterial partial pressure of oxygen/inspired fraction of oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) = 226-300]. Thirty-five percent of patients developed at least one organ failure (organ system component score ≥ 3), and the most common non-neurologic organ system failure was severe respiratory failure ($\text{PaO}_2/\text{FiO}_2 \leq 150$), occurring in 23% of patients. Other multicenter studies have also reported high incidence of extracerebral organ dysfunctions after TBI^[10] or SAH^[11]. These extracerebral organ failures, especially respiratory failure and ICU-acquired sepsis, seem to be more frequent in patients with brain injuries than in patients with non-neurologic conditions^[12].

Lung injuries are frequent and can lead to significant consequences for patients with brain injuries by

directly altering outcomes. Respiratory failure and mechanical ventilation appear to be risk factors for increased mortality and poor neurological outcomes in patients with brain injuries^[6-9] and are associated with longer ICU and hospital LOS^[4,5]. Pelosi *et al*^[13], in a recent prospective observational and multicenter study, described outcomes among mechanically ventilated patients with various types of brain injuries (362 patients with ischemic or hemorrhagic stroke and 190 patients with brain trauma) and compared them to non-neurologic patients. Respiratory failure was the most frequent extracerebral organ dysfunction in neurologic patients. Patients with neurologic disease who were mechanically ventilated had longer ICU and ventilator-days, more tracheostomy requirement, more VAP and higher mortality rates than non-neurologic patients.

VAP

Pneumonia and VAP are frequently encountered in neurologic patients due to decrease in the level of consciousness and massive aspiration or even microaspirations^[14]. Risk factors for developing VAP in brain-injured patients have been identified: polytransfusion, age, obesity, diabetes, immunocompromized status, chronic pulmonary disease and use of barbiturates^[15]. Moreover, mechanical ventilation, sedation and myorelaxant use, previous antibiotic therapy and the absence of proclive position during mechanical ventilation increase the risk of developing VAP^[16]. Additionally, brain injury-induced immunosuppression promotes the development of infectious diseases^[17-20].

The incidence of VAP in patients with severe TBI is 21% to 60%^[15,21,22]. *Methicillin-susceptible Staphylococcus aureus* is the most common pathogen reported in VAP in patients with severe TBI. Early enteral feeding and oral care has been shown to decrease the incidence of VAP in the neuro-ICU^[22,23]. Pelosi *et al*^[13] reported a higher rate of VAP in patients with TBI compared to patients with ischemic or hemorrhagic stroke and non-neurologic patients.

Cinotti *et al*^[24] reported a retrospective analysis of 193 patients with SAH who were mechanically ventilated. VAP occurred in 48.7% of the patients, and the main responsible pathogen was also *Methicillin-susceptible Staphylococcus aureus*. This study did not find an increase in the mortality for these patients, but a longer duration of mechanical ventilation and ICU LOS^[24]. Frontera *et al*^[25] analyzed data of 573 patients with SAH (with or without mechanical ventilation) and quantified the prevalence of nosocomial infectious complications. The most common complication was pneumonia with a prevalence of 20%. Pneumonia was an independent factor for mortality or severe disability at 3 mo^[25].

Kasuya *et al*^[26] observed a 28% rate of VAP in 111 stroke patients on mechanical ventilation. VAP prolonged the duration mechanical ventilation and ICU LOS. Chronic lung disease, National Institute of

Health Stroke Score at admission and hemorrhagic transformation were independent risk factors for VAP. The most common responsible bacteria were *Methicillin-resistant Staphylococcus aureus* and *Methicillin-susceptible Staphylococcus aureus*^[26]. In patients with severe ischemic stroke, VAP increased mortality by 3-fold^[27].

ARDS

ARDS occur with a high incidence rate in patients with brain injuries. The definition of ARDS used in most of the studies is the American-European consensus conference criteria^[28]. A recent study reported an incidence of 35% of ARDS in a cohort of 192 patients with neurologic disorders (hemorrhagic stroke, SAH, subdural hematoma, TBI and ischemic stroke)^[29]. Other studies have shown an ARDS incidence of 19% to 35% in patients with a glasgow coma scale (GCS) score < 9^[12,29,30].

Patients with isolated TBI present 20%-25% of ARDS^[31,32], and patients with SAH present 20%-38% of ARDS^[3,7,33]. A recent retrospective study conducted from 1994 to 2008 in the United States of America reported an incidence of ARDS in admissions of patients with acute ischemic stroke of 4%^[4]. Aspiration-related ARDS was diagnosed in 3.6% patients in another recent retrospective cohort study on 1495 patients with acute stroke^[34].

In all cases, ARDS impacts the morbidity and mortality of patients with brain injuries^[4,7,30,35,36]. Occurrence of ARDS after TBI leads to a 3-fold increase in hospital mortality^[32]. ARDS is an independent risk factor for increased mortality and poor neurologic outcomes and is associated with longer ICU and hospital LOS^[4,30]. Risk factors have been identified for the development of ARDS. First, the severity of the initial brain injury revealed by low Glasgow coma score (GCS 3-4) and initial cerebral computed tomography (CT) scan abnormalities (midline shift and global CT findings)^[31,35,36]. Secondly, induced hypertension, administration of vasoactive drugs and a history of drug abuse have been reported as independent factors for ARDS in severe TBI^[35]. Finally, general risk factors have been identified such as young age, male gender, ethnicity, history of chronic arterial hypertension, diabetes, chronic obstructive pulmonary disease, development of sepsis, cardiovascular, renal and hematological dysfunctions^[4,32,37]. Recently, Mascia *et al*^[30] described the ventilatory management of 82 patients with severe TBI in a prospective multicenter observational study. Twenty-two percent of the patients developed ARDS, and these patients initially had higher tidal volumes (Vt) than patients without ARDS. The proportion of ARDS increased with Vt settings in a dose-response relationship. In the days preceding ARDS, 72% of patients with ARDS had a mean Vt \geq 10 mL/kg predicted body weight (PBW)^[30]. The ventilator management of patients with severe TBI seems to be a

key point in ARDS development and fits into the "double hit" model which will be detailed later in this review.

The ARDS distribution over the time is bimodal, with an early peak on day 2-3 after the onset of mechanical ventilation and a later peak on day 7-8^[10], often related to pneumonia^[15].

NPE

NPE has been described for more than 100 years^[38]. It has been defined as a clinical entity with an acute onset of protein-rich lung edema after significant central nervous system injuries such as TBI, SAH, stroke, spinal cord injury, status epilepticus, meningitis or subdural hemorrhage and the exclusion of other plausible causes^[39-42].

In a review on NPE cases reported from 1990 to 2003, the most frequent neurologic injury was SAH (42.9%) and symptom onset was < 4 h after brain injury in 71.4% of patients. The mortality rate of NPE was high, nearing 10%, but patients who survived usually recover very quickly (< 72 h for 52.4%)^[41]. Rogers *et al*^[40] reported a large autopsy database of patients with head injuries who died at the scene or within 96 h of injury. The diagnosis of NPE included the presence of edema, congestion and hemorrhage associated with an increase in lung weight. The incidence of NPE in isolated TBI patients who died at the scene was 32%. It reached 50% for patients who died within 96 h. An inverse correlation between cerebral perfusion pressure and the PaO₂/FiO₂ ratio was observed, even if the chest X-ray was considered normal^[40]. The incidence of NPE in aneurysmal SAH varies from 2% to 25%^[11,43]. The incidence seems to be higher in fatal SAH^[44]. Risk factors identified are old age, delay to surgery, vertebral artery surgery and the severity of clinical and CT-scan scores (Hun-Hess and Fisher grades)^[11,45]. The occurrence of NPE after SAH is associated with poor outcomes and higher mortality^[46,47].

NPE can be considered as a form of ARDS with the consensus definition. So, some authors proposed the following diagnostic criteria: (1) bilateral infiltrates; (2) PaO₂/FiO₂ ratio < 200; (3) no evidence of left atrial hypertension; (4) presence of severe central nervous system injury that has caused increased intracranial pressure (ICP); and (5) absence of other common causes of ARDS (*e.g.*, aspiration, massive blood transfusion or sepsis)^[48].

PATHOPHYSIOLOGY OF BRAIN-LUNG CROSSTALK

Brain to lung pathway

The pathophysiology of lung injuries after an acute brain injury is still in debate, and several theories have been proposed; recently, the "double hit" model has been described^[1].

The sympathetic response to increased ICP has an important role. Some authors explained some parts

of NPE with neuro-cardiac and neuro-hemodynamic paradigms^[48]. It has been well demonstrated that direct myocardial injury with Takotsubo's cardiomyopathy, can participate to NPE^[49-51]. Massive sympathetic discharge following brain injuries seems to induce direct myocyte injuries with wall motion abnormalities that follow a pattern of sympathetic nerve innervation^[52]. The neuro-hemodynamic theory is defined by indirect ventricular compliance impairment resulting from rapid increases in systemic and pulmonary pressures. Indeed, translocation of blood flow from the highly resistant systemic circulation to the low resistance pulmonary circulation causes a hydrostatic form of pulmonary edema^[53]. Animal models have shown an increase in left atrial, systemic and pulmonary pressures associated with NPE^[54-56]. Although hydrostatic pressure and cardiac impairment most likely play a role in the pathogenesis of NPE, these theories do not explain the presence of red blood cells and protein in the alveolar fluid^[57].

The blast theory

Theodore and Robin first defined the "blast theory" of NPE as an impairment of vascular permeability^[58]. The transient increase of intravascular pressure, caused by an acute increase in ICP, damages the capillary-alveolar membrane. So, pulmonary endothelium injuries cause a leak of protein-rich plasma^[58]. This theory includes the coexistence of high hydrostatic pressure and pulmonary endothelium injury. Some degree of capillary hypertension seems necessary for the occurrence of this pulmonary edema, and a pressure-dependent increase in permeability may be a common point in NPE^[59,60]. Animal models have allowed the exploration of this theory. Maron *et al.*^[59] reported in canine isolated perfused lung lobes, a minimum of 70 torr of venous pressure is necessary to have protein permeability and to note a linear correlation between the increase in venous pressure and the osmotic reflection coefficient for total proteins^[59]. Bosso *et al.*^[60] explored the relationship between the degree of pulmonary hypertension and post-mortem extravascular lung water content (EVLW) in rabbits with intracranial hypertension. The pulmonary arterial pressure had to exceed 25 torr to observe an increase in extravascular lung water^[60]. In contrast, Bowers *et al.*^[61] determined the effects of intracranial hypertension in a sheep model by measuring the flow rate and protein content of lung lymph. They noted a constant increase in lung vascular permeability but with inconstant increase in pulmonary vascular pressure^[61]. Few reports are available in humans because hemodynamic monitoring at the time of the initial severe increase in ICP is rare. After this initial hemodynamic instability and massive sympathetic response, systemic and pulmonary pressures could return to normal values, whereas capillary-alveolar membrane damage persists^[58,62]. Some authors observed no changes in systemic pressure, despite the occurrence of NPE

underlying direct pulmonary endothelial damage following brain injury^[63]. This concept has been called "pulmonary venule adrenergic hypersensitivity".

Pulmonary venule adrenergic hypersensitivity

Some human cases with continuous hemodynamic monitoring reported NPE without hemodynamic instability^[63,64]. So, the NPE may result, in part, from select pulmonary venoconstriction after massive sympathetic discharge following brain injury. Pulmonary vessels have α - and β -adrenergic receptors that may be activated leading to endothelial integrity changes^[65]. Animal models demonstrate an increase in pulmonary vascular permeability and edema formation that could not be explained by hemodynamic changes alone^[61,66]. In anesthetized dogs with raised ICP, McClellan *et al.*^[66] noted a 3-fold increase in pulmonary vascular permeability (exudative edema) with a moderate increase in pulmonary arterial pressures and cardiac output. However, when they reproduced these hemodynamic changes in dogs without intracranial hypertension, they did not report any changes in the protein leak index^[66]. Peterson *et al.*^[67] administered α -adrenergic blockers to anesthetized sheep with progressive levels of intracranial hypertension. They reported the prevention of pulmonary edema formation with minor systemic arterial pressure effects supporting a direct adrenergic action on the pulmonary vascular bed^[67].

Double hit model

Systemic inflammatory response appeared to play a major role in the development of pulmonary failure after acute brain injury. This pathophysiological process completes the blast injury theory^[1,68]. Intracranial inflammatory response occurs after brain injury, and pro-inflammatory cytokines [interleukin 1 (IL-1), IL-6], tumor necrosis factor (TNF), IL-8] are produced locally in cerebral injured tissue^[69]. Microglia and astrocytes are the principal source of inflammatory mediators. Then, alteration of the blood brain barrier (BBB) permeability allows their discharge into the systemic circulation with a transcranial gradient. This could be responsible for extracerebral dysfunctions^[70-72]. This systemic production of inflammatory mediators constitutes an inflammatory environment: the "first hit". Organ are therefore more susceptible to subsequent events, the "second hit", such as mechanical ventilation, infections or surgical procedures, that are in normal condition harmless^[1] (Figure 1). López-Aguilar *et al.*^[73] randomized rabbits to control or brain injured group with a 120 min mechanical ventilation with the same ventilator settings followed by aggressive mechanical ventilation. In the brain-injured group, lungs had more changes in the ultrafiltration coefficient, weight and alveolar hemorrhage^[73]. Hyperactivated neutrophils and leukocyte-endothelial cell interactions could probably have contributed to this pathological process^[74]. Acute inflammatory response in both brain and lung after brain injury has been

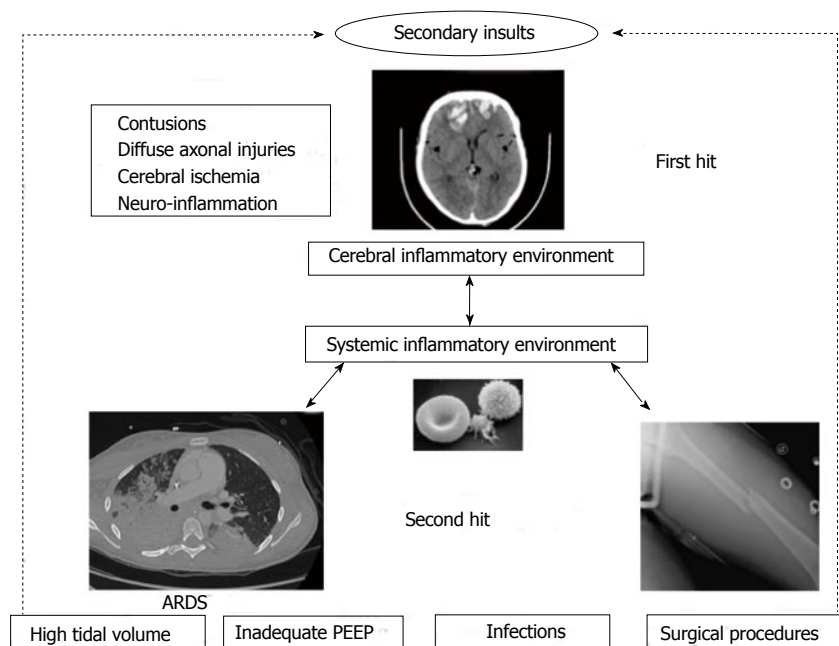


Figure 1 The double hit model in the context of brain injury. ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure.

shown in human and animal. Experimental intracerebral hemorrhage injury is accompanied by an increase in intracellular adhesion molecule-1 and tissue factor in both brain and lung. Progressive neutrophil recruitment and morphological pulmonary damage such as disruption of alveolar structures has been observed^[75]. Kalsotra *et al.*^[76] showed a large migration of macrophages and neutrophils in the major airways and alveolar spaces after brain injury in rats, with an increase of leukotriene B4 production within the lung^[76]. Brain-dead human donors have significantly higher IL-8 levels in the broncho-alveolar lavage compared to healthy subjects or ventilated non brain-dead patients. Moreover, neutrophil infiltration in the lungs well correlates with levels of IL-8^[77]. In a rat weight-drop model of TBI, ultrastructural damage in type II pneumocytes with important intracellular vacuoles and increased lipid peroxidation have been reported^[78]. Recently, Heuer *et al.*^[79] studied pigs with acute intracranial hypertension. They reported higher scores of inflammation, edema and necrosis in the lung and other organs compared with control pigs without intracranial hypertension despite the absence of hypoperfusion and hypoxemia^[79]. Previously, they compared 4 groups of pigs: control, with intracranial hypertension, with ARDS and with intracranial hypertension + ARDS. They analyzed lung CT-scans of each group. Intracranial hypertension alone increased lung density and exacerbated the increase in lung density in pigs with ARDS. Moreover, the gas-tissue ratio of the lung was decreased by intracranial hypertension in normal and injured lungs with an increase of poorly aerated and atelectatic lung areas. These lung CT-scan injuries were exacerbated by intracranial hypertension^[74].

The catecholamine storm, in conjunction with the

cerebral and systemic inflammatory reaction (first hit) creates an inflammatory environment leading to an increased susceptibility of the lung to further injurious events (second hit). This pathway could be the bed for lung injuries in patients with acute cerebral damage. However, this inflammatory cascade does not occur only in one way: from the brain to the lung, but also from the lung to the brain.

Hypothalamo-pituitary adrenal axis

Since several years, hypothalamo-pituitary adrenal axis [Hypothalamo-pituitary adrenal (HPA) axis] in brain injury has been explored in experimental and clinical studies and it could participate to lung dysfunction. Indeed, it has major effects on stress and systemic inflammatory response after trauma^[80,81]. In the initial phase of trauma, inflammation mediators, such as IL-6, activate massively HPA axis to induce an initial hypercortisolism, main effector of compensatory anti-inflammatory response syndrome^[80,82,83]. This hypercortisolism allow decreasing deleterious effects of inflammatory response, as its spread in organism and protect also other organs^[81,84]. Moreover, endogenous glucocorticoids stimulate anti-infectious immunity^[85] and HPA axis has major role in hemodynamic response and maintain of blood pressure^[86,87].

After TBI, 25%-50% of patients present an acute secondary adrenal insufficiency^[88-91]. These patients had worse outcomes and neurologic prognostic, lower arterial pressure, greater vasopressor use and higher mortality rate^[88,89,92,93]. Moreover, trauma-induced adrenal insufficiency is correlated with systemic inflammatory response syndrome^[94]. Patients with adrenal insufficiency have longer high plasma IL-6 levels than patients with normal adrenal response to

stress^[89,95]. In multiple-injured patients, persistence of high IL-6 plasma level at day 7 is associated with higher mortality rate and incidence of pneumonia^[96]. Persistence of systemic inflammatory response syndrome seems to be predictive of nosocomial infection in trauma patients^[97,98]. The principal theory is that secondary adrenal insufficiency exposes patients to deleterious effects of uncontrolled systemic inflammation with immunodepression, nosocomial infections, especially VAP and overwhelming inflammatory response^[90,98,99]. So this HAP axis dysfunction could participate to weaken the lung after TBI.

A multicenter, randomized trial reported in 150 intubated patients with severe trauma and corticosteroid insufficiency, a decrease risk of hospital-acquired pneumonia with stress-dose of hydrocortisone, particularly in the sub-group of patients with severe TBI^[100]. However, this result was not confirmed with recent trial in patients with severe TBI^[101]. Stroke-induced immunodepression has been described with HAP axis-related abnormalities following acute ischemic stroke^[102] and is probably implicated in high incidence of pneumonia^[103].

Lung to brain pathway

A complex pathway throughout autonomic, neuro-inflammatory, neuro-endocrine and immunologic systems has been described. This pathway is involved in normal physiology to contribute to maintain homeostasis, but may lead to adverse effects^[104]. Two components may be involved in this lung to brain pathway: lung injuries themselves, such as ARDS, and mechanical ventilation.

Lung injuries due to inadequate ventilator settings, could result in an inflammatory response, initially located in the lung parenchyma. But this could extend to the systemic circulation and then to other organs and the brain. Multi-organ failure can occur as a result of pulmonary injuries^[105]. The main cause of mortality in patients with ARDS is multiple organ failure and not hypoxemia or pulmonary dysfunction^[106]. It has been well described that ARDS survivors have cognitive deterioration including memory, language and cognitive decline^[107-109] and that patients with a long duration of mechanical ventilation present neurologic impairment with memory and cognitive alteration^[110]. The hippocampus, which is involved in learning and memory processes, is particularly vulnerable to hypoxia^[111]. However, ARDS can lead to hippocampal injuries with memory defects, regardless of the degree of hypoxia^[112]. ARDS, in the same way than septic shock, can induce neuronal damages. Nguyen *et al.*^[113] studied 170 patients with severe sepsis or septic shock in a prospective study. They found an increase in plasmatic marker of brain damages as S-100 β protein and neuron-specific enolase (NSE) in respectively 42% and 53% of these patients^[114]. High S-100 β protein levels were reported in patients with decreased consciousness and encephalopathy. In pig models of ARDS (lavage

model), S-100 β protein levels were significantly higher than in pigs with hypoxemia induced by lavage than when hypoxia was induced by reducing the inspired oxygen fraction^[115]. Moreover, histopathologic changes in the hippocampus occurred only in pigs with ARDS. The authors suggested that brain damage could only be observed in ARDS independently to hypoxemia. S-100 β protein and NSE might represent cerebral injuries and BBB alterations in patients with ARDS^[113]. Permeability of both the blood-brain and lung barriers can be altered by pathophysiologic situations and allows communication between the brain and the lung^[116].

Lung injuries may aggravate the sensitivity of the brain to acute injuries. In their previous study, Heuer *et al.*^[74] reported brain damage in pigs with ARDS alone and reciprocal synergistic effects between the lung and brain with worsening of brain damage in the group with ARDS + intracranial hypertension^[74]. Indeed, cerebral tissue oxygenation (PtiO₂) and brain tissue density (reflecting cerebral edema) decreased in all animals (intracranial hypertension, ARDS and ARDS + intracranial hypertension) compared to the control group. NSE and S-100 β protein levels increased significantly in all animals compared to the control group, but the most marked increase was in the group with ARDS, as for IL-1 β and IL-6. So ARDS could exacerbate cerebral damage in acute cerebral hypertension. Hegeman *et al.*^[105] described, after injurious stress and strain in the lung, inflammation of the alveoli, recruitment of neutrophils and production of cytokines. Endothelial cells, activated by cytokines, secrete chemokines and express adhesion molecules on their surface, leading to enhanced leukocyte adhesiveness and transmigration of active immune cells across the endothelium^[105]. This local inflammation can then spread into the systemic circulation. Lung inflammation could spread to the cerebral system through humoral, cellular and neural pathways^[116].

Beyond pulmonary injuries, mechanical ventilation strategies, used daily in the ICU, could impair regional blood flow and brain oxygenation. Indeed, Bickenbach *et al.*^[117] studied PtiO₂ and cerebral metabolism in a porcine model of ARDS over 8 h. Pigs were randomized in 2 groups: low tidal (LT) volume (6 mL/kg) and high tidal (HT) volume (12 mL/kg)^[117]. No differences between the two groups were found in terms of PaO₂, PaCO₂ and pH. ARDS induced a significant decrease in PtiO₂ in both groups, but the PtiO₂ increased significantly at 4 and 8 h in the LT group compared to the HT group. Lactates in microdialysis were higher in the HT group at 2, 4 and 8 h. After 2 h, the plasmatic S-100 protein level decreased in the LT group, and IL-6 increased in the HT group. Therefore, LT volume ventilation improved cerebral tissue oxygenation compared to HT volume ventilation in ARDS. HT volume ventilation could increase the inflammatory response and could impair cerebral oxygenation and metabolism. Quilez *et al.*^[118] studied the effect of Vt on activation in areas of

the brain in a rat model of MV with c-fos expression, a marker of neuronal activation. They randomized 3 groups of healthy-brain rats: basal (not submitted to mechanical ventilation), low Vt (8 mL/kg and positive end-expiratory pressure (PEEP) of 0 cmH₂O) and high Vt (30 mL/kg and PEEP of 0 cmH₂O). The inflammatory response (TNF- α) and c-fos expression in the retrosplenial cortex and thalamus were higher in the high Vt group than in the low Vt group^[118]. So, setting of mechanical ventilation can directly affect the brain, most likely *via* inflammatory mediators. These data highlight the importance of the ventilator setting in patients undergoing mechanical ventilation and particularly in brain injured patients.

THE CONFLICT BETWEEN THE LUNG AND THE BRAIN

Mechanical ventilation allows the supply of oxygen and the removal of carbon dioxide (CO₂) with tight control of the PaO₂ and PaCO₂, the goal is to prevent secondary cerebral ischemia and increase neurologic outcomes.

To prevent or limit Ventilation-Induced Lung Injury (VILI) the concept of protective ventilation has been developed using with low Vt, plateau pressure < 30 cmH₂O and adequate PEEP levels^[119]. VILI has been described as the results of 3 mechanisms: volotrauma, atelectrauma and biotrauma^[120,121]. Volotrauma results from overdistension of the lung parenchyma with a high Vt. Atelectrauma results from the recruitment-derecruitment of collapsed alveoli due to an inadequate PEEP level. Biotrauma comes from a local inflammatory process due to overdistending tidal volumes and repetitive opening and closing lung units. However, most of the studies that have enhanced ventilation strategy in ARDS patients have excluded brain-injured patients^[122-124]. The concept of "open the lung and keep it open" for ARDS with a low Vt, high PEEP and recruitment maneuvers, with permissive hypercapnia could have potential deleterious consequences on the brain, and intensivists are often fearful to use some parts of protective ventilation in patients with brain injury.

Tidal volume

The use of low Vt decreases systemic and pulmonary inflammatory responses in patients with ARDS^[124-126] but also in patients with inflammatory processes such as aspiration, sepsis, pneumonia or trauma^[127,128]. Mascia *et al.*^[30] reported that the proportion of ARDS in patients with severe TBI increased with higher initial tidal volume (Vt) settings in a dose-response relationship^[30]. The ventilator management of patients with severe TBI seems to be a key point of ARDS development. As we described before high Vt could affect the brain and could be an injurious event (second hit) in the lung that is particularly sensitive due to brain injury. There is no prospective study regarding the use of low Vt in TBI patients. However, recently, Krebs *et al.*^[129] reported in

rats with massive brain damage that a low Vt (6 mL/kg) with open lung PEEP (set according to the minimal static elastance of the respiratory system) compared to a high Vt (12 mL/kg) and low PEEP improved oxygenation reduced lung damage according to histology, genome analysis and real-time quantitative polymerase chain reaction with a decrease of IL-6^[129].

The protective mechanical ventilation for ARDS includes low Vt (6 mL/kg PBW) and then low minute ventilation, with consequently permissive hypercapnia. Cerebral effects of hypercapnia are well known (vasodilation) and should be avoided in case of intracranial hypertension^[130]. Objectives for the management of severe TBI are maintaining the PaCO₂ between 35 to 40 mmHg^[131] but this goal is sometimes not possible when using protective mechanical ventilation. Individualized management with neuromonitoring could allow us, in specific difficult cases, to use higher values of PaCO₂ and supervise its impact on brain homeostasis. A small retrospective study in 12 patients with SAH and ARDS reported no increase in ICP with lung protective ventilation and hypercapnia (50-60 mmHg)^[132]. Recently, Westermaier *et al.*^[133] performed a gradual increase of PaCO₂ to 40, 50 and 60 mmHg in patients with poor-grade SAH. Cerebral blood flow and brain tissue oxygen saturation (S_tO₂) reacted with sustained elevation without an increase in intracranial pressure^[133].

PEEP

Application of PEEP is part of the protective mechanical ventilation to recruit collapsed alveoli, improve PaO₂ and lung compliance^[134]. However, the use of PEEP may alter the cerebral blood flow by CO₂-mediated and hemodynamic repercussion^[135,136]. Therefore, Pelosi *et al.*^[13] reported in a prospective observational multicenter study that more than 80% of neurologic patients in the ICU were ventilated with a PEEP \leq 5 cmH₂O^[13]. PEEP is necessary to prevent collapse and/or recruit collapsed alveoli and thereby reduce atelectasis, especially when low Vt is used. Its application is also a key point of protective ventilation.

Some studies reported the effects of PEEP on cerebral hemodynamics. Mascia *et al.*^[137] randomly applied PEEP at 5 and 10 cmH₂O in 12 brain-injured patients with ARDS. Patients who were responders had decreased elastance and increased PaO₂, while patients who were non-responders had an increase of elastance and PaCO₂. Intracranial pressure and jugular saturation were constant in recruiters but increased in non-recruiters suggesting deleterious effects in this group^[137]. Therefore, the use of PEEP in brain-injured patients seems to be safe when patients are responders to the PEEP level (*i.e.*, not creating overdistension, increase in dead space and in PaCO₂)^[138]. When PEEP induces lung recruitment, intracranial pressure and cerebral perfusion do not change, and PaO₂ increases^[1]. PEEP could be safely used and must probably be used in brain-injured patients if the optimal PEEP is searched and adapted

individually, as for patients with ARDS and a healthy brain.

Muench *et al.*^[139] examined the influence of PEEP levels on intracranial pressure, P_{tO_2} , cerebral blood flow and systemic hemodynamics in healthy pigs and patients with SAH^[139]. High levels of PEEP did not influence cerebral parameters in pigs. In patients with SAH, changes in the regional cerebral blood flow were reported, resulting from arterial pressure changes and altered cerebral autoregulation. Normalization of systemic arterial pressure restored cerebral blood flow. Recently, Schramm *et al.*^[140] measured cerebral blood flow in 20 patients with ARDS. An increase in PEEP from 9 to 14 cmH₂O did not influence blood flow velocity. Caricato *et al.*^[141] examined the effect of respiratory system compliance on the intracranial effects of PEEP. No impact on cerebral and systemic hemodynamics were reported with 0, 5, 8 or 12 cmH₂O of PEEP^[141]. The use of PEEP appears to be safe, if arterial blood pressure is maintained. Euvolemia is probably a condition that can minimize the effect of PEEP on arterial blood pressure^[139,142,143].

Moreover, some authors recommend to optimize elevation of the head to enhance cerebro-venous drainage through the vertebral venous system, not subjected to intrathoracic pressure and to maintain PEEP lower than ICP to limit interference with venous outflow^[1,144,145].

An accurate monitoring of macrohemodynamic, respiratory system and cerebral parameters is needed to optimize the use of PEEP in brain-injured patients.

Recruitment maneuvers

Several studies in patients with ARDS recommended recruitment maneuvers (RM) to recruit collapsed pulmonary alveoli and open the lung followed by appropriate PEEP to maintain recruitment of the lung leading to improvement of oxygenation and compliance of the respiratory system^[146,147]. However, for the same reasons as PEEP, RM could decrease arterial blood pressure and increase ICP by interfering with venous blood return and causing an increase in intrathoracic pressure^[137]. Bein *et al.*^[148] reported in 11 patients with severe cerebral lesions (traumatic and non-traumatic) and ARDS, the effects of RM, which included sustaining 60 cmH₂O for 30 s^[148]. They recorded an increase in ICP, a decrease in mean arterial pressure, cerebral perfusion pressure (< 65 mmHg) and jugular oxygen saturation (< 55%) at the end of the RM. The improvement of arterial oxygenation was reported just after the RM but was not maintained after. Therefore, the authors did not recommend this maneuver. The impact on cerebral blood flow and intracranial pressure depends on the hemodynamic tolerance of RM. Re-aeration of lung units depends not only on the inflating pressure but also on the duration of sustained pressure (inflating pressure-time product)^[149-151]. Constantin *et al.*^[146] compared 2 RM: continuous airway pressure

(CPAP) with 40 cmH₂O for 40 s and extended sigh (eSigh) with PEEP maintained at 10 cmH₂O above the lower inflection point for 15 min^[146]. They reported that only eSigh increased recruited volume and that eSigh was hemodynamically better tolerated than CPAP and induced a greater and more prolonged increase in arterial oxygenation. Moreover, response to RM seems to depend on the lung morphology. Patients with diffuse loss of aeration are more responsive than patients with a focal loss of aeration^[152]. These parameters have to be considered before using RM. Therefore, eSigh may be better adapted to patients with severe brain injuries due to its better hemodynamic tolerance. Nemer *et al.*^[153] compared 2 RM: CPAP at 35 cmH₂O for 40 s and PEEP of 15 cmH₂O and pressure control above PEEP of 35 cmH₂O for 2 min in patients with SAH and ARDS^[153]. CPAP recruitment leads to higher intracranial pressure (> 20 mmHg) and lower cerebral perfusion pressure (< 65 mmHg). In another study, 28 RMs were performed in 9 patients with ARDS and cerebral injury in a stepwise with 3 cmH₂O increments and decrements of PEEP. No significant differences were found for mean arterial pressure, intracranial pressure and cerebral perfusion pressure after RMs compared with baseline values^[154]. Therefore the use of RM may be safe and possible with strict monitoring of systemic and cerebral parameters and use of progressive and soft maneuvers.

Wolf *et al.*^[155] evaluated the feasibility of the "open lung approach" with low tidal volume, a high level of PEEP and RM in 13 patients with acute brain injury and ARDS^[155]. They reported a decrease of FiO_2 from 0.85 to 0.55, 24 h after the first RM with an increase of PaO_2/FiO_2 from 142 to 257. In parallel, intracranial pressure, $PaCO_2$ and P_{tO_2} remained stable. The authors concluded that protective ventilation is safe in neurosurgical patients and improves oxygenation without side effects.

Prone position

Prone position has been used for 30 years in patients with ARDS. It has been proven to increase oxygenation with different mechanisms such as net recruitment, more homogeneous distribution of alveolar inflation and protection of VILI. Benefits in terms of outcomes and mortality have been shown in severely hypoxemic ARDS if a sufficient duration of prone position is used^[156-158]. This respiratory management has been sparsely studied in patients with cerebral injuries. Some authors reported cases or series of prone position^[159-161]. Reinprecht *et al.*^[159] analyzed the effect of this position in 16 patients with severe SAH and ARDS. They reported a significant increase in PaO_2 and P_{tO_2} with significant, but not deleterious, increases in intracranial pressure and decreases in cerebral perfusion pressure^[159]. A case report of a patient with severe traumatic chest and brain injuries showed improvement of oxygenation with a moderate, but very transient, increase in intracranial pressure after 20 h of prone position^[161].

The Table 1 summarizes the effects of different parts

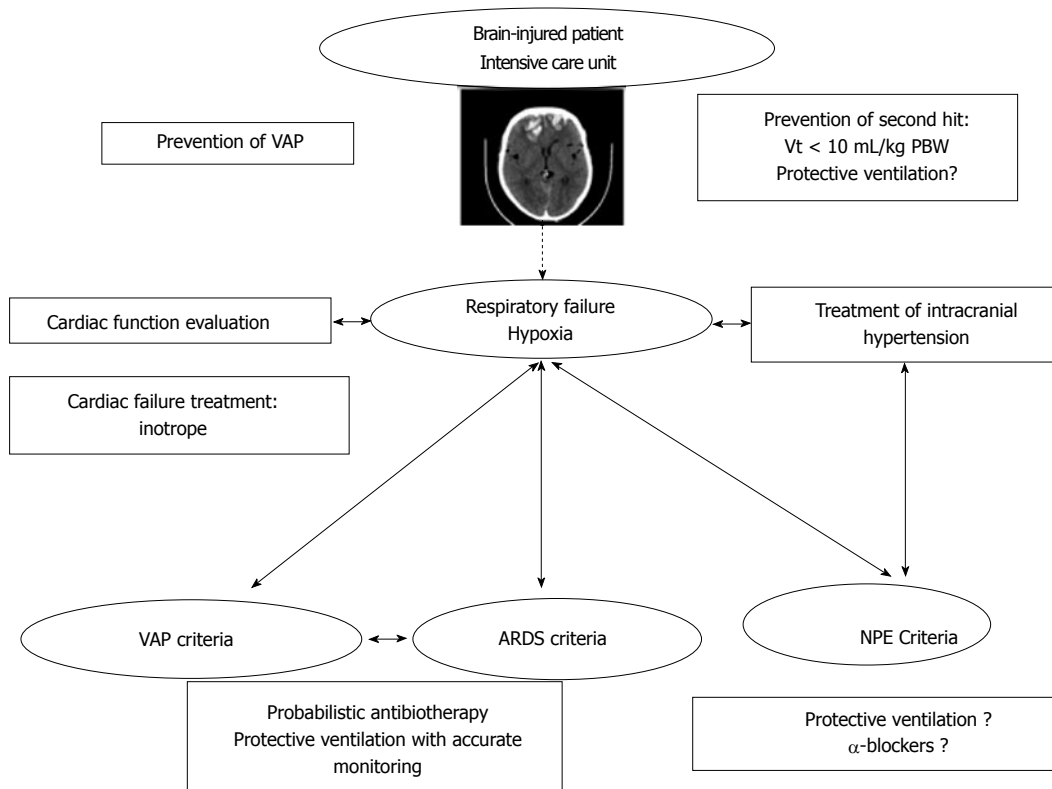


Figure 2 Algorithm approach for pulmonary dysfunction in brain-injured patient. ARDS: Acute respiratory distress syndrome; VAP: Ventilator-associated pneumonia; Vt: Tidal volume; PBW: Predictive body weight; NPE: Neurogenic pulmonary edema.

Table 1 Effects of protective ventilation on brain hemodynamic and metabolism

	CBF	ICP	CPP	P _r O ₂	SjO ₂	Lactates (microdialysis)
High Vt In pigs with ARDS ^[117]				↓		↑
Low Vt In pigs with ARDS ^[117]				↑		↓
Permissive hypercapnia (PaCO ₂ : 40-60 mmHg) in patients with SAH ^[132,133]	↑	=	=	↑		
PEEP	=	=	=			
	if MAP is maintained ^[140]	if responder patient ^[137] ↑ If non-responder patient ^[137] ↑ If MAP decreased ^[148]	if responder patient ^[137] ↓ If non-responder patient ^[137] ↓ If MAP decreased ^[148]			
RM					↓	
					If MAP decreased ^[148]	
Open lung approach (low Vt + high PEEP + RM) in patients with acute brain injury and ARDS ^[155]		=	=	=		

Responder patient to PEEP: Decrease in elastance and increased PaO₂; Non-responder patient to PEEP: Increase in elastance and PaCO₂. CBF: Cerebral blood flow; ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; P_rO₂: Cerebral tissue oxygenation; SjO₂: Jugular vein oxygen saturation; Vt: Tidal volume; PEEP: Positive end-expiratory pressure; RM: Recruitment maneuvers; MAP: Mean arterial pressure; ARDS: Acute respiratory distress syndrome.

of protective ventilation on brain hemodynamic and metabolism.

Alternative methods for tight CO₂ control and refractory hypoxia such as high frequency oscillatory ventilation and extracorporeal lung support techniques (percutaneous extracorporeal lung assist and extracorporeal membrane oxygenation) have been poorly

evaluated in patients with head injuries^[145].

CLINICAL MANAGEMENT OF LUNG INJURIES IN BRAIN-INJURED PATIENTS

In clinical practice, there is actually no recommendation for ventilator strategy of brain-injured patients except

for PaO₂ and PaCO₂ targets^[131].

Treatment of VAP is not specific for patients with cerebral injuries but it is important to note that prevention seems to be a key point. Treatment of VAP has to be started quickly as VAP is associated with higher mortality rate and poor neurologic outcome. It may follow the guidelines for hospital-acquired and VAP^[162]. Risk factors of VAP in brain-injured patients are numerous and prophylactic measures have to focus on these, including oral care^[23,103,163]. The high rate of VAP in brain-injured patients is, in part, explained by long duration of mechanical ventilation^[164]. So Roquilly *et al.*^[165] reported in a before/after evaluation of an extubation readiness bundle, a decrease of duration of mechanical ventilation in patients with brain injury^[165]. The bundle components were 1/protective ventilation (Vt: 6-8 mL/kg PBW, PEEP > 3 cmH₂O) 2/early enteral nutrition (initiation day 1 and 25 kCal/kg per day before day 3) 3/optimization of the probabilistic antibiotherapy for VAP and 4/a systematic approach of extubation (ventilator weaning and removal of tube if Glasgow Coma Scale ≥ 10 and cough). Despite a compliance with bundle elements of 21% in the intervention phase, they observed a reduction of duration of mechanical ventilation, rate of VAP and rate of unplanned extubation compared to the control observational phase. In acute stroke, the major measure is to avoid per os nutrition until swallowing is evaluated and validated^[166-168]. No difference has been found between percutaneous gastrostomy or nasal feeding tube in terms of rate of pneumonia but percutaneous gastrostomy tube seems to be safer and more effective for feeding^[169]. For TBI, in front of traumatic-induced adrenal insufficiency, the use of stress-dose steroids during initial management are still debated for prevention of VAP but literature doesn't allow us to provide an answer^[101].

Concerning NPE, few studies have reported specific treatment in humans. Some animal studies have focused on α -blockers treatment to limit massive sympathetic discharge after brain injuries^[48,170]. Two cases of human NPE were published about use of adrenergic blocker (phentolamine or chlorpromazine) and successful treatment with improvement of hemodynamic instability and oxygenation^[171,172]. Further studies are needed to explore this way. But the key point of NPE management is to treat the underlying cerebral injuries to decrease ICP, mitigate the sympathetic discharge and improve oxygenation^[41,48].

Concerning ARDS, protective ventilation has been largely discussed in the previous section. An accurate monitoring of macrohemodynamic, respiratory and cerebral parameters are needed to optimize the management.

When a brain-injured patient presents hypoxia, all diagnoses evoked in this review could be discussed. The Figure 2 summarizes different steps of management and prevention of respiratory failure in brain-injured patient. The response of the cardiopulmonary system varies widely among patients with brain injury (direct

myocardial injury, non-cardiogenic mechanisms, *etc.*). So first of all, it is important to evaluate cardiac function to adapt our management and initiate treatment of cardiogenic failure if necessary. Moreover, normalization of ICP is an important step to decrease sympathetic discharge and its consequences. Criteria of VAP, ARDS and NPE have to be researched and for some patients in which difference between NPE and ARDS could be difficult, measurement of serum catecholamines may be helpful^[48].

CONCLUSION

Brain and lung strongly interact *via* complex pathways. In cases of brain injury, therapeutic strategies should protect the brain but also the lung to avoid worsening of both brain and lung dysfunction. If correctly applied, mechanical ventilation could have beneficial effect on brain oxygenation, even if PEEP and recruitment maneuvers are used. Experimental and clinical studies are needed to explore pathophysiological processes and evaluate optimal ventilator setting in brain-injured patients with lung injuries. A strict monitoring of systemic, respiratory and cerebral parameters is probably required to optimize the management of these patients.

REFERENCES

- 1 **Mascia L.** Acute lung injury in patients with severe brain injury: a double hit model. *Neurocrit Care* 2009; **11**: 417-426 [PMID: 19548120 DOI: 10.1007/s12028-009-9242-8]
- 2 **Lee K, Rincon F.** Pulmonary complications in patients with severe brain injury. *Crit Care Res Pract* 2012; **2012**: 207247 [PMID: 23133746 DOI: 10.1155/2012/207247]
- 3 **Veeravagu A, Chen YR, Ludwig C, Rincon F, Maltenfort M, Jallo J, Choudhri O, Steinberg GK, Ratliff JK.** Acute lung injury in patients with subarachnoid hemorrhage: a nationwide inpatient sample study. *World Neurosurg* 2014; **82**: e235-e241 [PMID: 24560705 DOI: 10.1016/j.wneu.2014.02.030]
- 4 **Rincon F, Maltenfort M, Dey S, Ghosh S, Vibbert M, Urtecho J, Jallo J, Ratliff JK, McBride JW, Bell R.** The prevalence and impact of mortality of the acute respiratory distress syndrome on admissions of patients with ischemic stroke in the United States. *J Intensive Care Med* 2014; **29**: 357-364 [PMID: 23753254 DOI: 10.1177/0885066613491919]
- 5 **Maramattom BV, Weigand S, Reinalda M, Wijdsicks EF, Manno EM.** Pulmonary complications after intracerebral hemorrhage. *Neurocrit Care* 2006; **5**: 115-119 [PMID: 17099257]
- 6 **Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJ.** Non-neurologic organ dysfunction in severe traumatic brain injury. *Crit Care Med* 2005; **33**: 654-660 [PMID: 15753760 DOI: 10.1097/01.CCM.0000155911.01844.54]
- 7 **Kahn JM, Caldwell EC, Deem S, Newell DW, Heckbert SR, Rubenfeld GD.** Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome. *Crit Care Med* 2006; **34**: 196-202 [PMID: 16374174 DOI: 10.1097/01.CCM.0000194540.44020.8E]
- 8 **Santoli F, De Jonghe B, Hayon J, Tran B, Piperaud M, Merrer J, Outin H.** Mechanical ventilation in patients with acute ischemic stroke: survival and outcome at one year. *Intensive Care Med* 2001; **27**: 1141-1146 [PMID: 11534561 DOI: 10.1007/s001340100998]
- 9 **Roch A, Michelet P, Jullien AC, Thirion X, Bregeon F, Papazian L, Roche P, Pellet W, Auffray JP.** Long-term outcome in intensive

- care unit survivors after mechanical ventilation for intracerebral hemorrhage. *Crit Care Med* 2003; **31**: 2651-2656 [PMID: 14605538 DOI: 10.1097/01.CCM.0000094222.57803.B4]
- 10 **Piek J**, Chesnut RM, Marshall LF, van Berkum-Clark M, Klauber MR, Blunt BA, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. Extracranial complications of severe head injury. *J Neurosurg* 1992; **77**: 901-907 [PMID: 1432133 DOI: 10.3171/jns.1992.77.6.0901]
 - 11 **Solenski NJ**, Haley EC, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med* 1995; **23**: 1007-1017 [PMID: 7774210 DOI: 10.1097/00003246-199506000-00004]
 - 12 **Mascia L**, Sakr Y, Pasero D, Payen D, Reinhart K, Vincent JL. Extracranial complications in patients with acute brain injury: a post-hoc analysis of the SOAP study. *Intensive Care Med* 2008; **34**: 720-727 [PMID: 18175107 DOI: 10.1007/s00134-007-0974-7]
 - 13 **Pelosi P**, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymonds K, Apezteguia C, Desmery P, Hurtado J, Abroug F, Elizalde J, Tomicic V, Cakar N, Gonzalez M, Arabi Y, Moreno R, Esteban A. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med* 2011; **39**: 1482-1492 [PMID: 21378554 DOI: 10.1097/CCM.0b013e31821209a8]
 - 14 **Kollef MH**, Morrow LE, Niederman MS, Leeper KV, Anzueto A, Benz-Scott L, Rodino FJ. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest* 2006; **129**: 1210-1218 [PMID: 16685011 DOI: 10.1378/chest.129.5.1210]
 - 15 **Bronchard R**, Albaladejo P, Brezac G, Geffroy A, Seince PF, Morris W, Branger C, Marty J. Early onset pneumonia: risk factors and consequences in head trauma patients. *Anesthesiology* 2004; **100**: 234-239 [PMID: 14739794 DOI: 10.1097/00000542-20040200-000009]
 - 16 **American Thoracic Society**, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388-416 [PMID: 15699079 DOI: 10.1164/rccm.200405-644ST]
 - 17 **Chamorro Á**, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. *Nat Rev Neurol* 2012; **8**: 401-410 [PMID: 22664787 DOI: 10.1038/nrneurol.2012.98]
 - 18 **Dirnagl U**, Klehmet J, Braun JS, Harms H, Meisel C, Ziemssen T, Prass K, Meisel A. Stroke-induced immunodepression: experimental evidence and clinical relevance. *Stroke* 2007; **38**: 770-773 [PMID: 17261736 DOI: 10.1161/01.STR.0000251441.89665.bc]
 - 19 **Meisel C**, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci* 2005; **6**: 775-786 [PMID: 16163382 DOI: 10.1038/nrn1765]
 - 20 **Dziedzic T**, Slowik A, Szczudlik A. Nosocomial infections and immunity: lesson from brain-injured patients. *Crit Care* 2004; **8**: 266-270 [PMID: 15312209 DOI: 10.1186/cc2828]
 - 21 **Woratyła SP**, Morgan AS, Mackay L, Bernstein B, Barba C. Factors associated with early onset pneumonia in the severely brain-injured patient. *Conn Med* 1995; **59**: 643-647 [PMID: 8565507]
 - 22 **Lepelletier D**, Roquilly A, Demeure dit latte D, Mahe PJ, Loutrel O, Champin P, Corvec S, Naux E, Pinaud M, Lejus C, Asehnoune K. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J Neurosurg Anesthesiol* 2010; **22**: 32-37 [PMID: 20027012 DOI: 10.1097/ANA.0b013e3181bdf52f]
 - 23 **Fields LB**. Oral care intervention to reduce incidence of ventilator-associated pneumonia in the neurologic intensive care unit. *J Neurosci Nurs* 2008; **40**: 291-298 [PMID: 18856250 DOI: 10.1097/01376517-200810000-00007]
 - 24 **Cinotti R**, Dordonnat-Moynard A, Feuillet F, Roquilly A, Rondeau N, Lepelletier D, Caillon J, Asseray N, Blanloeil Y, Rozec B, Asehnoune K. Risk factors and pathogens involved in early ventilator-acquired pneumonia in patients with severe subarachnoid hemorrhage. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 823-830 [PMID: 24322991 DOI: 10.1007/s10096-013-2020-8]
 - 25 **Frontera JA**, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, Parra A, Connolly ES, Mayer SA. Impact of nosocomial infectious complications after subarachnoid hemorrhage. *Neurosurgery* 2008; **62**: 80-87; discussion 87 [PMID: 18300894 DOI: 10.1227/01.NEU.0000311064.18368.EA]
 - 26 **Kasuya Y**, Hargett JL, Lenhardt R, Heine MF, Doufas AG, Rimmel KS, Ramirez JA, Akça O. Ventilator-associated pneumonia in critically ill stroke patients: frequency, risk factors, and outcomes. *J Crit Care* 2011; **26**: 273-279 [PMID: 21106334 DOI: 10.1016/j.jcrc.2010.09.006]
 - 27 **Hilker R**, Poetter C, Findeisen N, Sobesky J, Jacobs A, Neveling M, Heiss WD. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. *Stroke* 2003; **34**: 975-981 [PMID: 12637700 DOI: 10.1161/01.STR.0000063373.70993.CD]
 - 28 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818-824 [PMID: 7509706 DOI: 10.1164/ajrccm.149.3.7509706]
 - 29 **Hoesch RE**, Lin E, Young M, Gottesman RF, Altaweel L, Nyquist PA, Stevens RD. Acute lung injury in critical neurological illness. *Crit Care Med* 2012; **40**: 587-593 [PMID: 21946655 DOI: 10.1097/CCM.0b013e3182545792]
 - 30 **Mascia L**, Zavala E, Bosma K, Pasero D, Decaroli D, Andrews P, Isnardi D, Davi A, Arguis MJ, Berardino M, Ducati A. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. *Crit Care Med* 2007; **35**: 1815-1820 [PMID: 17568331 DOI: 10.1097/01.CCM.0000275269.77467.DF]
 - 31 **Holland MC**, Mackersie RC, Morabito D, Campbell AR, Kivett VA, Patel R, Erickson VR, Pittet JF. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma* 2003; **55**: 106-111 [PMID: 12855888 DOI: 10.1097/01.TA.0000071620.27375.BE]
 - 32 **Rincon F**, Ghosh S, Dey S, Maltenfort M, Vibbert M, Urtecho J, McBride W, Moussouttas M, Bell R, Ratliff JK, Jallo J. Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the United States. *Neurosurgery* 2012; **71**: 795-803 [PMID: 22855028 DOI: 10.1227/NEU.0b013e3182672ae5]
 - 33 **Wartenberg KE**, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapkovich N, Parra A, Connolly ES, Mayer SA. Impact of medical complications on outcome after subarachnoid hemorrhage. *Crit Care Med* 2006; **34**: 617-623; quiz 624 [PMID: 16521258 DOI: 10.1097/00003246-200612002-00426]
 - 34 **Zhao JN**, Liu Y, Li HC. Aspiration-related acute respiratory distress syndrome in acute stroke patient. *PLoS One* 2015; **e0118682** [PMID: 25790377 DOI: 10.1371/journal.pone.0118682]
 - 35 **Contant CF**, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg* 2001; **95**: 560-568 [PMID: 11596949 DOI: 10.3171/jns.2001.95.4.0560]
 - 36 **Bratton SL**, Davis RL. Acute lung injury in isolated traumatic brain injury. *Neurosurgery* 1997; **40**: 707-712; discussion 712 [PMID: 9092843 DOI: 10.1097/00006123-199704000-00009]
 - 37 **Ghosh S**, Dey SK, Maltenfort M, Vibbert M, Urtecho J, Jallo J. Epidemiological Trends of Adult Respiratory Distress Syndrome (ARDS) After Traumatic Brain Injury in the United States. American Academy of Neurology, New Orleans, La, USA, 2012
 - 38 **Shanahan W**. Acute pulmonary edema as a complication of epileptic seizures. *NY Med J* 1908; **37**: 54-56
 - 39 **Simmons RL**, Heisterkamp CA, Collins JA, Genslar S, Martin AM. Respiratory insufficiency in combat casualties. 3. Arterial hypoxemia after wounding. *Ann Surg* 1969; **170**: 45-52 [PMID: 5789529 DOI: 10.1097/00000658-196907000-00006]
 - 40 **Rogers FB**, Shackford SR, Trevisani GT, Davis JW, Mackersie RC, Hoyt DB. Neurogenic pulmonary edema in fatal and nonfatal head injuries. *J Trauma* 1995; **39**: 860-866; discussion 866-868 [PMID: 7474001 DOI: 10.1097/00005373-199511000-00009]

- 41 **Fontes RB**, Aguiar PH, Zanetti MV, Andrade F, Mandel M, Teixeira MJ. Acute neurogenic pulmonary edema: case reports and literature review. *J Neurosurg Anesthesiol* 2003; **15**: 144-150 [PMID: 12658001 DOI: 10.1097/00008506-200304000-00013]
- 42 **Baumann A**, Audibert G, McDonnell J, Mertes PM. Neurogenic pulmonary edema. *Acta Anaesthesiol Scand* 2007; **51**: 447-455 [PMID: 17378783 DOI: 10.1111/j.1399-6576.2007.01276.x]
- 43 **Friedman JA**, Pichelmann MA, Piegras DG, McIver JI, Toussaint LG, McClelland RL, Nichols DA, Meyer FB, Atkinson JL, Wijdicks EF. Pulmonary complications of aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2003; **52**: 1025-1031; discussion 1031-1032 [PMID: 12699543]
- 44 **Weir BK**. Pulmonary edema following fatal aneurysm rupture. *J Neurosurg* 1978; **49**: 502-507 [PMID: 690677 DOI: 10.3171/jns.1978.49.4.0502]
- 45 **Ochiai H**, Yamakawa Y, Kubota E. Deformation of the ventrolateral medulla oblongata by subarachnoid hemorrhage from ruptured vertebral artery aneurysms causes neurogenic pulmonary edema. *Neurol Med Chir (Tokyo)* 2001; **41**: 529-534; discussion 534-535 [PMID: 11758704]
- 46 **Fein IA**, Rackow EC. Neurogenic pulmonary edema. *Chest* 1982; **81**: 318-320 [PMID: 7056107 DOI: 10.1378/chest.81.3.318]
- 47 **Mayer SA**, Fink ME, Homma S, Sherman D, LiMandri G, Lennihan L, Solomon RA, Klebanoff LM, Beckford A, Raps EC. Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. *Neurology* 1994; **44**: 815-820 [PMID: 8190280 DOI: 10.1212/WNL.44.5.815]
- 48 **Davison DL**, Terek M, Chawla LS. Neurogenic pulmonary edema. *Crit Care* 2012; **16**: 212 [PMID: 22429697 DOI: 10.1186/cc11226]
- 49 **Bahloul M**, Chaari AN, Kallel H, Khabir A, Ayadi A, Charfeddine H, Hergafi L, Chaari AD, Chelly HE, Ben Hamida C, Rekik N, Bouaziz M. Neurogenic pulmonary edema due to traumatic brain injury: evidence of cardiac dysfunction. *Am J Crit Care* 2006; **15**: 462-470 [PMID: 16926367]
- 50 **Connor RC**. Myocardial damage secondary to brain lesions. *Am Heart J* 1969; **78**: 145-148 [PMID: 5797266 DOI: 10.1016/0002-8703(69)90001-5]
- 51 **Mayer SA**, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, Fink ME, Beckford A, Klebanoff LM. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke* 1999; **30**: 780-786 [PMID: 10187879 DOI: 10.1161/01.STR.30.4.780]
- 52 **Zaroff JG**, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. *J Am Soc Echocardiogr* 2000; **13**: 774-779 [PMID: 10936822 DOI: 10.1067/mje.2000.105763]
- 53 **SARNOFF SJ**, SARNOFF LC. Neurohemodynamics of pulmonary edema. II. The role of sympathetic pathways in the elevation of pulmonary and stemic vascular pressures following the intracisternal injection of fibrin. *Circulation* 1952; **6**: 51-62 [PMID: 14936200 DOI: 10.1161/01.CIR.6.1.51]
- 54 **Ducker TB**, Simmons RL. Increased intracranial pressure and pulmonary edema. 2. The hemodynamic response of dogs and monkeys to increased intracranial pressure. *J Neurosurg* 1968; **28**: 118-123 [PMID: 4966167 DOI: 10.3171/jns.1968.28.2.0118]
- 55 **Brashear RE**, Ross JC. Hemodynamic effects of elevated cerebrospinal fluid pressure: alterations with adrenergic blockade. *J Clin Invest* 1970; **49**: 1324-1333 [PMID: 4393489 DOI: 10.1172/JCI106348]
- 56 **Minnear FL**, Kite C, Hill LA, van der Zee H. Endothelial injury and pulmonary congestion characterize neurogenic pulmonary edema in rabbits. *J Appl Physiol* (1985) 1987; **63**: 335-341 [PMID: 3114222]
- 57 **van der Zee H**, Malik AB, Lee BC, Hakim TS. Lung fluid and protein exchange during intracranial hypertension and role of sympathetic mechanisms. *J Appl Physiol Respir Environ Exerc Physiol* 1980; **48**: 273-280 [PMID: 7364612]
- 58 **Theodore J**, Robin ED. Speculations on neurogenic pulmonary edema (NPE). *Am Rev Respir Dis* 1976; **113**: 405-411 [PMID: 178254]
- 59 **Maron MB**. Effect of elevated vascular pressure transients on protein permeability in the lung. *J Appl Physiol* (1985) 1989; **67**: 305-310 [PMID: 2759957]
- 60 **Bosso FJ**, Lang SA, Maron MB. Role of hemodynamics and vagus nerves in development of fibrin-induced pulmonary edema. *J Appl Physiol* (1985) 1990; **69**: 2227-2232 [PMID: 2077021]
- 61 **Bowers RE**, McKeen CR, Park BE, Brigham KL. Increased pulmonary vascular permeability follows intracranial hypertension in sheep. *Am Rev Respir Dis* 1979; **119**: 637-641 [PMID: 443634]
- 62 **Melon E**, Bonnet F, Lepresle E, Fevrier MJ, Djindjian M, François Y, Gray F, Debras C. Altered capillary permeability in neurogenic pulmonary oedema. *Intensive Care Med* 1985; **11**: 323-325 [PMID: 4086709 DOI: 10.1007/BF00273546]
- 63 **Keegan MT**, Lanier WL. Pulmonary edema after resection of a fourth ventricle tumor: possible evidence for a medulla-mediated mechanism. *Mayo Clin Proc* 1999; **74**: 264-268 [PMID: 10089996 DOI: 10.4065/74.3.264]
- 64 **Fein A**, Grossman RF, Jones JG, Overland E, Pitts L, Murray JF, Staub NC. The value of edema fluid protein measurement in patients with pulmonary edema. *Am J Med* 1979; **67**: 32-38 [PMID: 463915 DOI: 10.1016/0002-9343(79)90066-4]
- 65 **Richardson JB**. Innervation of the pulmonary circulation: an overview. *The Pulmonary Circulation in Health and Disease*, 1987: 9-14
- 66 **McClellan MD**, Dauber IM, Weil JV. Elevated intracranial pressure increases pulmonary vascular permeability to protein. *J Appl Physiol* (1985) 1989; **67**: 1185-1191 [PMID: 2793711]
- 67 **Peterson BT**, Ross JC, Brigham KL. Effect of naloxone on the pulmonary vascular responses to graded levels of intracranial hypertension in anesthetized sheep. *Am Rev Respir Dis* 1983; **128**: 1024-1029 [PMID: 6650974]
- 68 **Avlonitis VS**, Fisher AJ, Kirby JA, Dark JH. Pulmonary transplantation: the role of brain death in donor lung injury. *Transplantation* 2003; **75**: 1928-1933 [PMID: 12829889 DOI: 10.1097/01.TP.0000066351.87480.9E]
- 69 **Ott L**, McClain CJ, Gillespie M, Young B. Cytokines and metabolic dysfunction after severe head injury. *J Neurotrauma* 1994; **11**: 447-472 [PMID: 7861440 DOI: 10.1089/neu.1994.11.447]
- 70 **Habgood MD**, Bye N, Dziegielewska KM, Ek CJ, Lane MA, Potter A, Morganti-Kossmann C, Saunders NR. Changes in blood-brain barrier permeability to large and small molecules following traumatic brain injury in mice. *Eur J Neurosci* 2007; **25**: 231-238 [PMID: 17241284 DOI: 10.1111/j.1460-9568.2006.05275.x]
- 71 **Morganti-Kossmann MC**, Rancan M, Stahel PF, Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care* 2002; **8**: 101-105 [PMID: 12386508 DOI: 10.1097/00075198-200204000-00002]
- 72 **McKeating EG**, Andrews PJ, Signorini DF, Mascia L. Transcranial cytokine gradients in patients requiring intensive care after acute brain injury. *Br J Anaesth* 1997; **78**: 520-523 [PMID: 9175965 DOI: 10.1093/bja/78.5.520]
- 73 **López-Aguilar J**, Villagrà A, Bernabé F, Murias G, Piacentini E, Real J, Fernández-Segoviano P, Romero PV, Hotchkiss JR, Blanch L. Massive brain injury enhances lung damage in an isolated lung model of ventilator-induced lung injury. *Crit Care Med* 2005; **33**: 1077-1083 [PMID: 15891339 DOI: 10.1097/01.CCM.0000162913.72479.F7]
- 74 **Heuer JF**, Pelosi P, Hermann P, Perske C, Crozier TA, Brück W, Quintel M. Acute effects of intracranial hypertension and ARDS on pulmonary and neuronal damage: a randomized experimental study in pigs. *Intensive Care Med* 2011; **37**: 1182-1191 [PMID: 21544692 DOI: 10.1007/s00134-011-2232-2]
- 75 **Wu S**, Fang CX, Kim J, Ren J. Enhanced pulmonary inflammation following experimental intracerebral hemorrhage. *Exp Neurol* 2006; **200**: 245-249 [PMID: 16516197 DOI: 10.1016/j.expneurol.2006.01.027]
- 76 **Kalsotra A**, Zhao J, Anakk S, Dash PK, Strobel HW. Brain trauma leads to enhanced lung inflammation and injury: evidence for role of P4504Fs in resolution. *J Cereb Blood Flow Metab* 2007; **27**:

- 963-974 [PMID: 16985506]
- 77 **Fisher AJ**, Donnelly SC, Hirani N, Burdick MD, Strieter RM, Dark JH, Corris PA. Enhanced pulmonary inflammation in organ donors following fatal non-traumatic brain injury. *Lancet* 1999; **353**: 1412-1413 [PMID: 10227229 DOI: 10.1016/S0140-6736(99)00494-8]
- 78 **Yildirim E**, Solaroglu I, Okutan O, Ozisik K, Kaptanoglu E, Sargon MF, Sakinci U. Ultrastructural changes in tracheobronchial epithelia following experimental traumatic brain injury in rats: protective effect of erythropoietin. *J Heart Lung Transplant* 2004; **23**: 1423-1429 [PMID: 15607673 DOI: 10.1016/j.healun.2003.10.006]
- 79 **Heuer JF**, Selke M, Crozier TA, Pelosi P, Herrmann P, Perske C, Quintel M. Effects of acute intracranial hypertension on extracerebral organs: a randomized experimental study in pigs. *J Neurol Surg A Cent Eur Neurosurg* 2012; **73**: 289-295 [PMID: 22899228 DOI: 10.1055/s-0032-1304813]
- 80 **Bone RC**. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 1996; **24**: 1125-1128 [PMID: 8674323 DOI: 10.1097/00003246-199607000-00010]
- 81 **Munford RS**, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med* 2001; **163**: 316-321 [PMID: 11179099 DOI: 10.1164/ajrccm.163.2.2007102]
- 82 **Offner PJ**, Moore EE, Ciesla D. The adrenal response after severe trauma. *Am J Surg* 2002; **184**: 649-653; discussion 653-654 [PMID: 12488202]
- 83 **Chrousos GP**. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; **332**: 1351-1362 [PMID: 7715646 DOI: 10.1056/NEJM199505183322008]
- 84 **Moore FA**, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma* 1996; **40**: 501-510; discussion 510-512 [PMID: 8614027]
- 85 **Webster JI**, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. *Annu Rev Immunol* 2002; **20**: 125-163 [PMID: 11861600 DOI: 10.1146/annurev.immunol.20.082401.104914]
- 86 **Rhen T**, Cidlowski JA. Antiinflammatory action of glucocorticoids-new mechanisms for old drugs. *N Engl J Med* 2005; **353**: 1711-1723 [PMID: 16236742 DOI: 10.1056/NEJMra050541]
- 87 **Prigent H**, Maxime V, Annane D. Clinical review: corticotherapy in sepsis. *Crit Care* 2004; **8**: 122-129 [PMID: 15025773 DOI: 10.1186/cc2374]
- 88 **Cohan P**, Wang C, McArthur DL, Cook SW, Dusick JR, Armin B, Swerdloff R, Vespa P, Muizelaar JP, Cryer HG, Christenson PD, Kelly DF. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. *Crit Care Med* 2005; **33**: 2358-2366 [PMID: 16215393 DOI: 10.1097/01.CCM.0000181735.51183.A7]
- 89 **Dimopoulou I**, Tsagarakis S, Kouyialis AT, Roussou P, Assithianakis G, Christoforaki M, Ilias I, Sakas DE, Thalassinou N, Roussos C. Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: incidence, pathophysiology, and relationship to vasopressor dependence and peripheral interleukin-6 levels. *Crit Care Med* 2004; **32**: 404-408 [PMID: 14758155 DOI: 10.1097/01.CCM.0000108885.37811.CA]
- 90 **Dimopoulou I**, Tsagarakis S, Theodorakopoulou M, Douka E, Zervou M, Kouyialis AT, Thalassinou N, Roussos C. Endocrine abnormalities in critical care patients with moderate-to-severe head trauma: incidence, pattern and predisposing factors. *Intensive Care Med* 2004; **30**: 1051-1057 [PMID: 15069597 DOI: 10.1007/s00134-004-2257-x]
- 91 **Llompert-Pou JA**, Raurich JM, Pérez-Bárcena J, Barceló A, Ibáñez J, Ayestarán JI. Acute Hypothalamic-pituitary-adrenal response in traumatic brain injury with and without extracerebral trauma. *Neurocrit Care* 2008; **9**: 230-236 [PMID: 18551387 DOI: 10.1007/s12028-008-9115-6]
- 92 **Mesotten D**, Vanhorebeek I, Van den Berghe G. The altered adrenal axis and treatment with glucocorticoids during critical illness. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 496-505 [PMID: 18695699 DOI: 10.1038/ncpendmet0921]
- 93 **Agha A**, Rogers B, Mylotte D, Taleb F, Tormey W, Phillips J, Thompson CJ. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. *Clin Endocrinol (Oxf)* 2004; **60**: 584-591 [PMID: 15104561 DOI: 10.1111/j.1365-2265.2004.02023.x]
- 94 **Hoehn S**, Asehnoune K, Brailly-Tabard S, Mazoit JX, Benhamou D, Moine P, Edouard AR. Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. *Anesthesiology* 2002; **97**: 807-813 [PMID: 12357144 DOI: 10.1097/0000542-200210000-00010]
- 95 **Papanicolaou DA**, Tsigos C, Oldfield EH, Chrousos GP. Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency? *J Clin Endocrinol Metab* 1996; **81**: 2303-2306 [PMID: 8964868 DOI: 10.1210/jcem.81.6.8964868]
- 96 **Gebhard F**, Pfetsch H, Steinbach G, Strecker W, Kinzl L, Brückner UB. Is interleukin 6 an early marker of injury severity following major trauma in humans? *Arch Surg* 2000; **135**: 291-295 [PMID: 10722030 DOI: 10.1001/archsurg.135.3.291]
- 97 **Bochicchio GV**, Napolitano LM, Joshi M, McCarter RJ, Scalea TM. Systemic inflammatory response syndrome score at admission independently predicts infection in blunt trauma patients. *J Trauma* 2001; **50**: 817-820 [PMID: 11379594 DOI: 10.1097/00005373-200105000-00007]
- 98 **Hoover L**, Bochicchio GV, Napolitano LM, Joshi M, Bochicchio K, Meyer W, Scalea TM. Systemic inflammatory response syndrome and nosocomial infection in trauma. *J Trauma* 2006; **61**: 310-316; discussion 316-317 [PMID: 16917443 DOI: 10.1097/01.ta.0000229052.75460.c2]
- 99 **Giannoudis PV**. Current concepts of the inflammatory response after major trauma: an update. *Injury* 2003; **34**: 397-404 [PMID: 12767787 DOI: 10.1016/S0020-1383(02)00416-3]
- 100 **Roquilly A**, Mahe PJ, Seguin P, Guittion C, Floch H, Tellier AC, Merson L, Renard B, Malledant Y, Flet L, Seville V, Volteau C, Masson D, Nguyen JM, Lejus C, Asehnoune K. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. *JAMA* 2011; **305**: 1201-1209 [PMID: 21427372 DOI: 10.1001/jama.2011.360]
- 101 **Asehnoune K**, Seguin P, Allary J, Feuillet F, Lasocki S, Cook F, Floch H, Chabanne R, Geeraerts T, Roger C, Perrigault PF, Hanouz JL, Lukaszewicz AC, Biais M, Boucheix P, Dahyot-Fizelier C, Capdevila X, Mahe PJ, Le Maguet P, Paugam-Burtz C, Gergaud S, Plaud B, Constantin JM, Malledant Y, Flet L, Seville V, Roquilly A. Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial. *Lancet Respir Med* 2014; **2**: 706-716 [PMID: 25066331 DOI: 10.1016/S2213-2600(14)70144-4]
- 102 **Marklund N**, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. *J Intern Med* 2004; **256**: 15-21 [PMID: 15189361 DOI: 10.1111/j.1365-2796.2004.01334.x]
- 103 **Hannawi Y**, Hannawi B, Rao CP, Suarez JJ, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. *Cerebrovasc Dis* 2013; **35**: 430-443 [PMID: 23735757 DOI: 10.1159/000350199]
- 104 **Stevens RD**, Puybasset L. The brain-lung-brain axis. *Intensive Care Med* 2011; **37**: 1054-1056 [PMID: 21544691 DOI: 10.1007/s00134-011-2233-1]
- 105 **Hegeman MA**, Hennis MP, Heijnen CJ, Specht PA, Lachmann B, Jansen NJ, van Vught AJ, Cobelens PM. Ventilator-induced endothelial activation and inflammation in the lung and distal organs. *Crit Care* 2009; **13**: R182 [PMID: 19917112 DOI: 10.1186/cc8168]
- 106 **Slutsky AS**, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 1998; **157**: 1721-1725 [PMID: 9620897 DOI: 10.1164/ajrccm.157.6.9709092]
- 107 **Hopkins RO**, Brett S. Chronic neurocognitive effects of critical illness. *Curr Opin Crit Care* 2005; **11**: 369-375 [PMID: 16015118 DOI: 10.1097/01.ccx.0000166399.88635.a5]
- 108 **Milbrandt EB**, Angus DC. Potential mechanisms and markers of critical illness-associated cognitive dysfunction. *Curr Opin*

- Crit Care* 2005; **11**: 355-359 [PMID: 16015116 DOI: 10.1097/01.ccx.0000170508.63067.04]
- 109 **Hopkins RO**, Jackson JC. Long-term neurocognitive function after critical illness. *Chest* 2006; **130**: 869-878 [PMID: 16963688 DOI: 10.1378/chest.130.3.869]
 - 110 **Pustavoitau A**, Stevens RD. Mechanisms of neurologic failure in critical illness. *Crit Care Clin* 2008; **24**: 1-24, vii [PMID: 18241776 DOI: 10.1016/j.ccc.2007.11.004]
 - 111 **Neves G**, Cooke SF, Bliss TV. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nat Rev Neurosci* 2008; **9**: 65-75 [PMID: 18094707 DOI: 10.1038/nrn2303]
 - 112 **Janz DR**, Abel TW, Jackson JC, Gunther ML, Heckers S, Ely EW. Brain autopsy findings in intensive care unit patients previously suffering from delirium: a pilot study. *J Crit Care* 2010; **25**: 538.e7-538.12 [PMID: 20580199]
 - 113 **Nguyen DN**, Spapen H, Su F, Schiettecatte J, Shi L, Hachimi-Idrissi S, Huyghens L. Elevated serum levels of S-100beta protein and neuron-specific enolase are associated with brain injury in patients with severe sepsis and septic shock. *Crit Care Med* 2006; **34**: 1967-1974 [PMID: 16607230 DOI: 10.1097/01.CCM.0000217218.51381.49]
 - 114 **Mrozek S**, Dumurgier J, Citerio G, Mebazaa A, Geeraerts T. Biomarkers and acute brain injuries: interest and limits. *Crit Care* 2014; **18**: 220 [PMID: 25029344 DOI: 10.1186/cc13841]
 - 115 **Fries M**, Bickenbach J, Henzler D, Beckers S, Dembinski R, Sellhaus B, Rossaint R, Kuhlen R. S-100 protein and neurohistopathologic changes in a porcine model of acute lung injury. *Anesthesiology* 2005; **102**: 761-767 [PMID: 15791105 DOI: 10.1097/00005542-200504000-00011]
 - 116 **López-Aguilar J**, Fernández-Gonzalo MS, Turon M, Quílez ME, Gómez-Simón V, Jódar MM, Blanch L. Lung-brain interaction in the mechanically ventilated patient. *Med Intensiva* 2013; **37**: 485-492 [PMID: 23260265 DOI: 10.1016/j.medine.2012.10.016]
 - 117 **Bickenbach J**, Zoremba N, Fries M, Dembinski R, Doering R, Ogawa E, Rossaint R, Kuhlen R. Low tidal volume ventilation in a porcine model of acute lung injury improves cerebral tissue oxygenation. *Anesth Analg* 2009; **109**: 847-855 [PMID: 19690257 DOI: 10.1213/ane.0b013e3181ad5769]
 - 118 **Quílez ME**, Fuster G, Villar J, Flores C, Martí-Sistac O, Blanch L, López-Aguilar J. Injurious mechanical ventilation affects neuronal activation in ventilated rats. *Crit Care* 2011; **15**: R124 [PMID: 21569477 DOI: 10.1186/cc10230]
 - 119 **Slutsky AS**. Lung injury caused by mechanical ventilation. *Chest* 1999; **116**: 9S-15S [PMID: 10424561 DOI: 10.1378/chest.116.suppl_1.9S-a]
 - 120 **Gattinoni L**, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. *Crit Care Med* 2010; **38**: S539-S548 [PMID: 21164395 DOI: 10.1097/CCM.0b013e3181f1fcf7]
 - 121 **Tremblay LN**, Slutsky AS. Ventilator-induced injury: from barotrauma to biotrauma. *Proc Assoc Am Physicians* 1998; **110**: 482-488 [PMID: 9824530]
 - 122 **Mercat A**, Richard JC, Vieille B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299**: 646-655 [PMID: 18270353 DOI: 10.1001/jama.299.6.646]
 - 123 **Meade MO**, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299**: 637-645 [PMID: 18270352 DOI: 10.1001/jama.299.6.637]
 - 124 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
 - 125 **Ranieri VM**, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999; **282**: 54-61 [PMID: 10404912 DOI: 10.1001/jama.282.1.54]
 - 126 **Ranieri VM**, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000; **284**: 43-44 [PMID: 10872010 DOI: 10.1001/jama.284.1.43]
 - 127 **Gajic O**, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; **32**: 1817-1824 [PMID: 15343007 DOI: 10.1097/01.CCM.0000133019.52531.30]
 - 128 **Gajic O**, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med* 2005; **31**: 922-926 [PMID: 15856172 DOI: 10.1007/s00134-005-2625-1]
 - 129 **Krebs J**, Tsagogiorgas C, Pelosi P, Rocco PR, Hottenrott M, Sticht C, Yard B, Luecke T. Open lung approach with low tidal volume mechanical ventilation attenuates lung injury in rats with massive brain damage. *Crit Care* 2014; **18**: R59 [PMID: 24693992 DOI: 10.1186/cc13813]
 - 130 **Ainslie PN**, Duffin J. Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol* 2009; **296**: R1473-R1495 [PMID: 19211719 DOI: 10.1152/ajpregu.91008.2008]
 - 131 **Brain Trauma Foundation**, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007; **24** Suppl 1: S1-106 [PMID: 17511534]
 - 132 **Petridis AK**, Doukas A, Kienke S, Maslehaty H, Mahvash M, Barth H, Mehdorn HM. The effect of lung-protective permissive hypercapnia in intracerebral pressure in patients with subarachnoid haemorrhage and ARDS. A retrospective study. *Acta Neurochir (Wien)* 2010; **152**: 2143-2145 [PMID: 20700747 DOI: 10.1007/s00701-010-0761-z]
 - 133 **Westermaier T**, Stetter C, Kunze E, Willner N, Holzmeier J, Kilgenstein C, Lee JY, Ernestus RI, Roewer N, Muellenbach RM. Controlled transient hypercapnia: a novel approach for the treatment of delayed cerebral ischemia after subarachnoid hemorrhage? *J Neurosurg* 2014; **121**: 1056-1062 [PMID: 25148012 DOI: 10.3171/2014.7.JNS132611]
 - 134 **Ranieri VM**, Eissa NT, Corbeil C, Chassé M, Braidly J, Matar N, Milic-Emili J. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1991; **144**: 544-551 [PMID: 1892293 DOI: 10.1164/ajrccm/144.3_Pt_1.544]
 - 135 **Blanch L**, Fernández R, Benito S, Mancebo J, Net A. Effect of PEEP on the arterial minus end-tidal carbon dioxide gradient. *Chest* 1987; **92**: 451-454 [PMID: 3113834 DOI: 10.1378/chest.92.3.451]
 - 136 **Doblar DD**, Santiago TV, Kahn AU, Edelman NH. The effect of positive end-expiratory pressure ventilation (PEEP) on cerebral blood flow and cerebrospinal fluid pressure in goats. *Anesthesiology* 1981; **55**: 244-250 [PMID: 6791528 DOI: 10.1097/00005542-198109000-00010]
 - 137 **Mascia L**, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. *Intensive Care Med* 2005; **31**: 373-379 [PMID: 15668765 DOI: 10.1007/s00134-004-2491-2]
 - 138 **Lou M**, Xue F, Chen L, Xue Y, Wang K. Is high PEEP ventilation strategy safe for acute respiratory distress syndrome after severe traumatic brain injury? *Brain Inj* 2012; **26**: 887-890 [PMID: 22583180]
 - 139 **Muench E**, Bauhuf C, Roth H, Horn P, Phillips M, Marquetant N, Quintel M, Vajkoczy P. Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain

- tissue oxygenation. *Crit Care Med* 2005; **33**: 2367-2372 [PMID: 16215394 DOI: 10.1097/01.CCM.0000181732.37319.DF]
- 140 **Schramm P**, Closhen D, Felkel M, Berres M, Klein KU, David M, Werner C, Engelhard K. Influence of PEEP on cerebral blood flow and cerebrovascular autoregulation in patients with acute respiratory distress syndrome. *J Neurosurg Anesthesiol* 2013; **25**: 162-167 [PMID: 23211642 DOI: 10.1097/ANA.0b013e31827c2f46]
 - 141 **Caricato A**, Conti G, Della Corte F, Mancino A, Santilli F, Sandroni C, Proietti R, Antonelli M. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. *J Trauma* 2005; **58**: 571-576 [PMID: 15761353 DOI: 10.1097/01.TA.0000152806.19198.DB]
 - 142 **Georgiadis D**, Schwarz S, Baumgartner RW, Veltkamp R, Schwab S. Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke. *Stroke* 2001; **32**: 2088-2092 [PMID: 11546901 DOI: 10.1161/hs0901.095406]
 - 143 **McGuire G**, Crossley D, Richards J, Wong D. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med* 1997; **25**: 1059-1062 [PMID: 9201061 DOI: 10.1097/00003246-199706000-00025]
 - 144 **Toung TJ**, Aizawa H, Traystman RJ. Effects of positive end-expiratory pressure ventilation on cerebral venous pressure with head elevation in dogs. *J Appl Physiol* (1985) 2000; **88**: 655-661 [PMID: 10658034]
 - 145 **Mazzeo AT**, Fanelli V, Mascia L. Brain-lung crosstalk in critical care: how protective mechanical ventilation can affect the brain homeostasis. *Minerva Anesthesiol* 2013; **79**: 299-309 [PMID: 23254163]
 - 146 **Constantin JM**, Jaber S, Futier E, Cayot-Constantin S, Verny-Pic M, Jung B, Bailly A, Guerin R, Bazin JE. Respiratory effects of different recruitment maneuvers in acute respiratory distress syndrome. *Crit Care* 2008; **12**: R50 [PMID: 18416847 DOI: 10.1186/cc6869]
 - 147 **Badet M**, Bayle F, Richard JC, Guérin C. Comparison of optimal positive end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury/acute respiratory distress syndrome. *Respir Care* 2009; **54**: 847-854 [PMID: 19558735 DOI: 10.4187/002013209793800448]
 - 148 **Bein T**, Kuhr LP, Bele S, Ploner F, Keyl C, Taeger K. Lung recruitment maneuver in patients with cerebral injury: effects on intracranial pressure and cerebral metabolism. *Intensive Care Med* 2002; **28**: 554-558 [PMID: 12029401 DOI: 10.1007/s00134-002-1273-y]
 - 149 **Marini JJ**. A lung-protective approach to ventilating ARDS. *Respir Care Clin N Am* 1998; **4**: 633-663, viii [PMID: 9881397]
 - 150 **Sydow M**, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J Respir Crit Care Med* 1994; **149**: 1550-1556 [PMID: 8004312 DOI: 10.1164/ajrcm.149.6.8004312]
 - 151 **Neumann P**, Berglund JE, Mondéjar EF, Magnusson A, Hedenstierna G. Effect of different pressure levels on the dynamics of lung collapse and recruitment in oleic-acid-induced lung injury. *Am J Respir Crit Care Med* 1998; **158**: 1636-1643 [PMID: 9817719 DOI: 10.1164/ajrcm.158.5.9711095]
 - 152 **Constantin JM**, Cayot-Constantin S, Roszyk L, Futier E, Sapin V, Dastugue B, Bazin JE, Rouby JJ. Response to recruitment maneuver influences net alveolar fluid clearance in acute respiratory distress syndrome. *Anesthesiology* 2007; **106**: 944-951 [PMID: 17457125 DOI: 10.1097/01.anes.0000265153.17062.64]
 - 153 **Nemer SN**, Caldeira JB, Azeredo LM, Garcia JM, Silva RT, Prado D, Santos RG, Guimarães BS, Ramos RA, Noé RA, Souza PC. Alveolar recruitment maneuver in patients with subarachnoid hemorrhage and acute respiratory distress syndrome: a comparison of 2 approaches. *J Crit Care* 2011; **26**: 22-27 [PMID: 20646904 DOI: 10.1016/j.jcrc.2010.04.015]
 - 154 **Zhang XY**, Yang ZJ, Wang QX, Fan HR. Impact of positive end-expiratory pressure on cerebral injury patients with hypoxemia. *Am J Emerg Med* 2011; **29**: 699-703 [PMID: 20825872 DOI: 10.1016/j.ajem.2010.01.042]
 - 155 **Wolf S**, Plev DV, Trost HA, Lumenta CB. Open lung ventilation in neurosurgery: an update on brain tissue oxygenation. *Acta Neurochir Suppl* 2005; **95**: 103-105 [PMID: 16463830]
 - 156 **Gattinoni L**, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. *Minerva Anesthesiol* 2010; **76**: 448-454 [PMID: 20473258]
 - 157 **Guérin C**, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. *Intensive Care Med* 2014; **40**: 1634-1642 [PMID: 25266133 DOI: 10.1007/s00134-014-3500-8]
 - 158 **Lee JM**, Bae W, Lee YJ, Cho YJ. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014; **42**: 1252-1262 [PMID: 24368348 DOI: 10.1097/CCM.0000000000000122]
 - 159 **Reinprecht A**, Greher M, Wolfsberger S, Dietrich W, Illievich UM, Gruber A. Prone position in subarachnoid hemorrhage patients with acute respiratory distress syndrome: effects on cerebral tissue oxygenation and intracranial pressure. *Crit Care Med* 2003; **31**: 1831-1838 [PMID: 12794427 DOI: 10.1097/01.CCM.0000063453.93855.0A]
 - 160 **Gritti P**, Lanterna LA, Re M, Martchenko S, Olivotto P, Brembilla C, Agostinis C, Paganoni G, Lorini FL. The use of inhaled nitric oxide and prone position in an ARDS patient with severe traumatic brain injury during spine stabilization. *J Anesth* 2013; **27**: 293-297 [PMID: 23065049 DOI: 10.1007/s00540-012-1495-2]
 - 161 **Ashtown-Cleary DT**, Duffy MR. Prone ventilation for refractory hypoxaemia in a patient with severe chest wall disruption and traumatic brain injury. *Br J Anaesth* 2011; **107**: 1009-1010 [PMID: 22088877 DOI: 10.1093/bja/aer374]
 - 162 **Torres A**, Ferrer M, Badia JR. Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. *Clin Infect Dis* 2010; **51** Suppl 1: S48-S53 [PMID: 20597672 DOI: 10.1086/653049]
 - 163 **O'Grady NP**, Murray PR, Ames N. Preventing ventilator-associated pneumonia: does the evidence support the practice? *JAMA* 2012; **307**: 2534-2539 [PMID: 22797453 DOI: 10.1001/jama.2012.6445]
 - 164 **Esteban A**, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287**: 345-355 [PMID: 11790214 DOI: 10.1001/jama.287.3.345]
 - 165 **Roquilly A**, Cinotti R, Jaber S, Vourc'h M, Pengam F, Mahe PJ, Lakhal K, Demeure D, Latte D, Rondeau N, Loutrel O, Paulus J, Rozec B, Blanloeil Y, Vibet MA, Sebillé V, Feuillet F, Asehnoune K. Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients: a before-after evaluation of a quality improvement project. *Am J Respir Crit Care Med* 2013; **188**: 958-966 [PMID: 23927561 DOI: 10.1164/rccm.201301-0116OC]
 - 166 **Adams HP**, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 2007; **115**: e478-e534 [PMID: 17515473 DOI: 10.1161/CIRCULATIONAHA.107.181486]
 - 167 **Ickenstein GW**, Riecker A, Höhlig C, Müller R, Becker U, Reichmann H, Prosiegel M. Pneumonia and in-hospital mortality in the context of neurogenic oropharyngeal dysphagia (NOD) in stroke

- and a new NOD step-wise concept. *J Neurol* 2010; **257**: 1492-1499 [PMID: 20383519 DOI: 10.1007/s00415-010-5558-8]
- 168 **Hinchey JA**, Shephard T, Furie K, Smith D, Wang D, Tonn S. Formal dysphagia screening protocols prevent pneumonia. *Stroke* 2005; **36**: 1972-1976 [PMID: 16109909 DOI: 10.1161/01.STR.0000177529.86868.8d]
- 169 **Gomes CA**, Lustosa SA, Matos D, Andriolo RB, Waisberg DR, Waisberg J. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. *Cochrane Database Syst Rev* 2012; **3**: CD008096 [PMID: 22419328]
- 170 **Lu WH**, Hsieh KS, Lu PJ, Wu YS, Ho WY, Cheng PW, Lai CC, Hsiao M, Tseng CJ. Different impacts of α - and β -blockers in neurogenic hypertension produced by brainstem lesions in rat. *Anesthesiology* 2014; **120**: 1192-1204 [PMID: 24614323 DOI: 10.1097/ALN.0000000000000218]
- 171 **Davison DL**, Chawla LS, Selassie L, Tevar R, Junker C, Seneff MG. Neurogenic pulmonary edema: successful treatment with IV phentolamine. *Chest* 2012; **141**: 793-795 [PMID: 22396565 DOI: 10.1378/chest.11-0789]
- 172 **Wohns RN**, Tamas L, Pierce KR, Howe JF. Chlorpromazine treatment for neurogenic pulmonary edema. *Crit Care Med* 1985; **13**: 210-211 [PMID: 2857630 DOI: 10.1097/00003246-198503000-00016]

P- Reviewer: Tanriverdi F, Tanabe S **S- Editor:** Ji FF **L- Editor:** A
E- Editor: Wu HL



Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function

Emer P Reeves, Cormac McCarthy, Oliver J McElvaney, Maya Sakthi N Vijayan, Michelle M White, Danielle M Dunlea, Kerstin Pohl, Noreen Lacey, Noel G McElvaney

Emer P Reeves, Cormac McCarthy, Oliver J McElvaney, Maya Sakthi N Vijayan, Michelle M White, Danielle M Dunlea, Kerstin Pohl, Noreen Lacey, Noel G McElvaney, Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland

Author contributions: All the authors equally contributed to this work.

Supported by The United States Cystic Fibrosis Foundation and Science Foundation Ireland under the Research Frontiers Programme (11/RFP/BMT/3094).

Conflict-of-interest statement: The authors declare no competing financial interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. Emer P Reeves, PhD, MSc, Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland. emerreeves@rcsi.ie
Telephone: +353-1-8093877
Fax: +353-1-8093808

Received: November 26, 2014
Peer-review started: November 26, 2014
First decision: December 12, 2014
Revised: January 10, 2015
Accepted: April 8, 2015
Article in press: April 9 2015
Published online: August 4, 2015

Abstract

Cystic fibrosis (CF) is a multisystem disorder with significantly shortened life expectancy. The major cause of mortality and morbidity is lung disease with increasing pulmonary exacerbations and decline in lung function predicting significantly poorer outcomes. The pathogenesis of lung disease in CF is characterised in part by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. This leads to accumulation of viscous mucus in the CF airway, providing an ideal environment for bacterial pathogens to grow and colonise, propagating airway inflammation in CF. The use of nebulised hypertonic saline (HTS) treatments has been shown to improve mucus clearance in CF and impact positively upon exacerbations, quality of life, and lung function. Several mechanisms of HTS likely improve outcome, resulting in clinically relevant enhancement in disease parameters related to increase in mucociliary clearance. There is increasing evidence to suggest that HTS is also beneficial through its anti-inflammatory properties and its ability to reduce bacterial activity and biofilm formation. This review will first describe the use of HTS in treatment of CF focusing on its efficacy and tolerability. The emphasis will then change to the potential benefits of aerosolized HTS for the attenuation of receptor mediated neutrophil functions, including down-regulation of oxidative burst activity, adhesion molecule expression, and the suppression of neutrophil degranulation of proteolytic enzymes.

Key words: Cystic fibrosis; Hypertonic saline; Mucociliary clearance; Neutrophils and inflammation

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The pathogenesis of lung disease in cystic

fibrosis (CF) is characterised by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. Therapies acting against airway mucus in CF include aerosolized hypertonic saline (HTS). It has been shown that HTS aids mucociliary clearance by restoring the liquid layer lining the airways. However, recent studies are beginning to broaden our view on the beneficial effects of HTS, which now extend to include anti-inflammatory properties. This review aims to discuss the therapeutic benefits of HTS and to identify the potential benefits of aerosolized HTS for attenuation of neutrophil function.

Reeves EP, McCarthy C, McElvaney OJ, Vijayan MSN, White MM, Dunlea DM, Pohl K, Lacey N, McElvaney NG. Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function. *World J Crit Care Med* 2015; 4(3): 179-191 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/179.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.179>

INTRODUCTION TO CYSTIC FIBROSIS AND THE ROLE OF NEUTROPHILS IN DEVELOPING AIRWAYS DISEASE

Cystic fibrosis (CF) is a complex genetic disease leading to increased risk of chronic lung disease resulting in terminal respiratory failure^[1,2]. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) chloride channel. Over 1900 CFTR mutations leading to defective chloride transport have been identified to date^[3] and result in misfolding of the CFTR protein. Reported mutations can be categorised into different classes depending on whether the mutation alters CFTR processing (Classes I, II and V) or results in dysregulated chloride secretion (Classes III, IV, VI) (Figure 1). The most common mutation is deletion of phenylalanine at position 508 ($\Delta F508$) which occurs in approximately 70% of patients with CF, and 90% of CF sufferers carry one copy^[4]. Defects in CFTR protein function not only impact upon cAMP-dependent chloride secretion but also result in increased epithelial sodium channel (ENaC)-mediated ion absorption in the superficial airway epithelium^[5,6]. CFTR absence or malfunction causes increased water re-absorption across airway epithelial cells leading to dehydration of the airway surface liquid (ASL) layer, persistent mucus hypersecretion and airflow obstruction^[7]. Dehydration of the airway surface liquid layer and mucus accumulation has been implicated in exacerbated airway inflammation^[8] and decline in lung function predicts significantly poorer outcomes^[9]. Therapeutic interventions to improve mucus clearance is a necessary treatment in CF^[10]. Hypertonic saline (HTS) at concentrations of 3% or higher is widely used to improve mucociliary clearance, as this increases

the tonicity of the ASL creating an osmotic gradient drawing water into the airway hence improving ASL and facilitating removal of airway secretions (Figure 2). Furthermore, HTS improves lung function and quality of life and significantly decreases the frequency of exacerbations^[11,12] and is generally well tolerated.

When considering the different immune cells present in the CF lung it has been documented that neutrophils account for approximately 60%-70% of immune cells in CF airway samples^[13]. Key studies have demonstrated that infiltration of neutrophils into the airways occurs early in the course of CF lung disease and that neutrophil-released granule proteins, particularly neutrophil elastase (NE), play a crucial pathological role^[14,15]. The expression of functional CFTR on the plasma membrane of neutrophils has been the topic of great debate^[16-19] with studies specifying intrinsic abnormalities due to a lack of CFTR function^[20,21]. Reports on reprogrammed cell activity secondary to chronic bacterial infection and inflammation have also been documented^[22]. Moreover, persistent mTOR and CREB pathway activation in CF airway neutrophils^[23] and augmented cell surface nutrient transporter expression are consistent with metabolic adaptation^[24].

Regardless of the cause of impaired neutrophil activity however, the fundamental consequence is neutrophil mediated tissue proteolysis. Excessive neutrophil recruitment to the lung, results in prolific NE degrading protease activity and inflammation that can eventually become chronic and lead to tissue destruction. The recognition that aerosolized HTS may moderate neutrophil cytotoxicity and may function to restrain an exuberant inflammatory response in CF, provides a possible strategy for mitigating inappropriate neutrophil activity. This review will initially describe the use of HTS in treatment of CF and then extend the focus of HTS beyond mucociliary, to the potential benefits of aerosolized hyperosmolar therapy for the modulation of neutrophil activity within the confines of the CF airways. Our review of the literature was carried out using the MEDLINE database (from 1976 to the year 2014), Google Scholar and The Cochrane Library databases using several appropriate generic terms.

CLINICAL EFFICACY OF NEBULISED HTS IN CF

The use of HTS treatments has been shown to improve mucus clearance in CF and impact upon exacerbations, quality of life and improve lung function^[12]. Early studies demonstrated an acute dose-response relationship between inhaled saline concentration and mucociliary clearance^[25], with short-term HTS administration improving mucociliary clearance and lung function with acceptable tolerability^[26]. In 2006, the National Hypertonic Saline in Cystic Fibrosis Study Group provided the first evidence for the long-term efficacy of HTS in individuals with CF. The study randomised

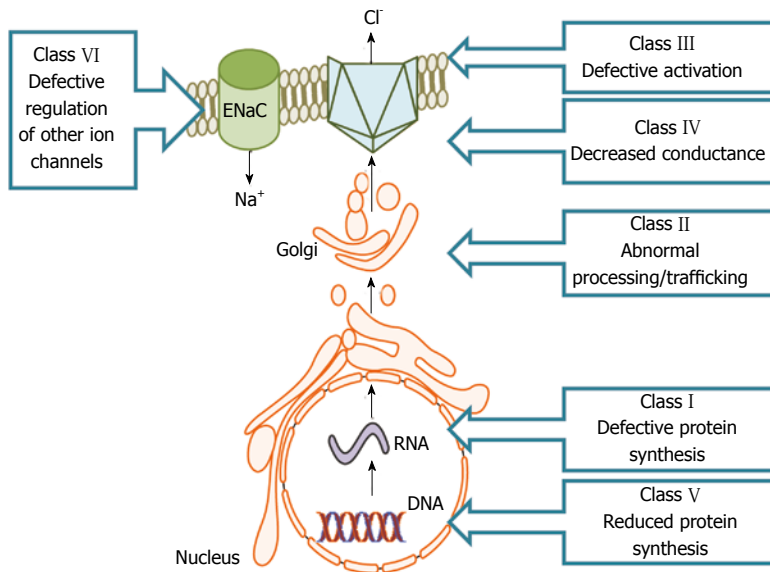


Figure 1 Classification of cystic fibrosis transmembrane conductance regulator mutations. CFTR mutations are classified into six groups according to their effect on CFTR function. Class I mutations affect biosynthesis, while class II mutations affect protein processing. Milder mutations such as class II to Class V impair CFTR channel function. CFTR: Cystic fibrosis transmembrane conductance regulator.

164 patients with CF to receive HTS (7%) or isotonic (0.9%) saline for 48 wk. Using forced vital capacity and forced expiratory volume in 1 s (FEV1) to assess the rate of change of lung function, no significant difference was observed between the two groups, but there was a statistically significant difference in the absolute change in lung function. More importantly, this study demonstrated an impressive reduction in the frequency of exacerbations in the HTS group, with fewer days missed from work or school. Furthermore, significant improvements in quality of life were observed, particularly with regard to mental health on quality of life questionnaires after long-term HTS therapy^[12].

A further study by Donaldson *et al.*^[26] showed that repeated use of 7% HTS generated both acute and sustained improvements in mucociliary clearance while improving FEV1 following four-times-daily treatment for 14 d, when compared to HTS given in conjunction with the ENaC inhibitor amiloride, however this study lacked a 0.9% saline control group, and as a result the effect of HTS could only be compared to patient baselines. Robinson *et al.*^[27], in a study employing radioaerosol technique, examined the acute effect of a single administration by aerosolization of 7% HTS, amiloride, or a combination of HTS and amiloride, or a 0.9% saline control. Results demonstrated that treatment with HTS alone significantly increased mucociliary clearance compared to treatment with HTS/amiloride combined, and both of these therapies were in turn significantly more effective than isotonic saline or amiloride alone.

The efficacy of HTS in improving mucociliary clearance may also be related to the volume administered as studies of 4 mL or 5 mL aerosolized HTS^[12,26] recorded smaller improvements in lung function compared to a 10 mL volume^[11,28]. In 2011, Dmello *et al.*^[29] used a multivariate logistic regression analysis to assess 340 CF exacerbations, 99 of them involving treatment with HTS. The results confirmed the beneficial effect of HTS with regard to reduction of pulmonary exacerbation frequency, even in those with "severe" CF lung disease,

categorised as those with an FEV1 below 40%. A further study, on the use of HTS during hospitalization for adult exacerbations of CF showed that nebulized treatment accelerated the recovery of FEV1 to baseline^[30]. However, there is conflicting evidence on the effectiveness of HTS upon lung function and FEV1 and a Cochrane review summarising all clinical trials of HTS in CF demonstrated a significant but minimal increase in FEV1 with a mean change of 4.15% after 4 wk, however at 48 wk this was not significant and was reduced to 2.31%^[31].

While spirometry, primarily FEV1, represents the measure of lung function used in the majority of HTS studies to date, the use of lung clearance index (LCI), a measure of ventilation inhomogeneity derived from the multiple breath washout test, is increasingly being employed for the early detection of CF respiratory disease^[32]. LCI has been shown to be a better predictor of later lung function abnormalities than FEV1^[33] and also correlates well with structural changes^[34,35]. LCI has been shown to detect treatment responses to HTS in children with CF aged 6-18 years who have normal baseline spirometry^[36]. It should be noted that while these studies when analysed together formed the basis for HTS use in the majority of CF centres in Europe and North America, the data for the most part only apply to adults, with a relative lack of evidence for use in children. Studies of HTS use in the CF child population have shown satisfactory safety and tolerability profiles^[37-39], but it is still unclear as to whether or not HTS treatment confers a clinical benefit upon this group. This may be in part due to the fact that younger individuals typically have less-advanced lung disease, nonetheless it is still well tolerated even in very young children aged between 12 and 30 mo^[38]. Although there is good evidence to suggest that HTS is of benefit regarding the enhancement of mucociliary clearance in adults, one study of HTS in CF children aged between 7-14 years published by Laube *et al.*^[40] demonstrated only negligible acute clearance effects, however, it should

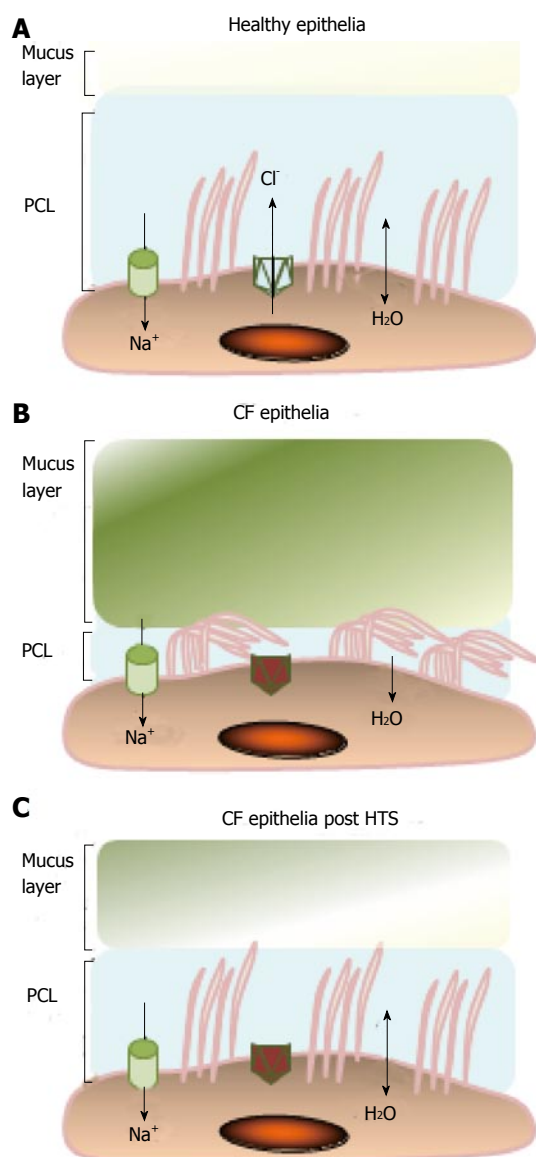


Figure 2 Effects of hypertonic saline on the airway surface liquid in cystic fibrosis. A: In healthy airway epithelia, CFTR plays a vital role in regulating hydration of the airway surface liquid (ASL) constructed of the periciliary layer (PCL) and the mucus layer; B: Due to defective CFTR in individuals with CF, Cl^- secretion is impaired and Na^+ absorption through ENaC is increased resulting in dehydration of the ASL and accumulation of thick mucus causing reduced PCL height; C: Treatment with hypertonic saline assists osmosis of water into the ASL and thus rehydrates the mucus and partially restores the PCL allowing for easier clearance of mucus. CFTR: Cystic fibrosis transmembrane conductance regulator.

be noted, that this was a single-dose study. A recent trial, from the North Carolina group at Chapel Hill, of HTS in CF children with normal lung function has shown some interesting results. This trial compares 6% HTS to 0.12% saline, with both arms of the study receiving 4 mL three times daily for four weeks. While mucociliary clearance was largely unaltered at 2 h after the initial dose, a significant acceleration of mucociliary clearance lasting greater than 12 h following the final dose was observed^[41]. This sustained effect suggests that single-dose studies may not be ideal predictors of mucociliary clearance in these individuals. A further study, by Amin

et al.^[36] using LCI to evaluate ventilation heterogeneity in individuals aged between 6 and 18 years with CF with normal spirometry, demonstrated a significant improvement in ventilation after four weeks of HTS treatment. Moreover, recent evidence has demonstrated that HTS is also beneficial through its ability to reduce *Pseudomonas aeruginosa* activity^[42] and also to disrupt biofilm formation^[43].

TOLERABILITY OF HTS IN CYSTIC FIBROSIS

Although an acute dose-response relationship between inhaled saline concentration and mucociliary clearance exists, data showing better or worse clinical efficacy with concentrations other than 7% are lacking. In this regard most clinical trials show that both 3% and 7% HTS are more effective than placebo^[31], however one clinical trial in a paediatric population demonstrated a superior effect with 3% HTS. In this study, the 3% group had significantly higher FEV1 on day 14 and day 28 compared to the group receiving 7%^[44], however this study was not extended beyond 28 d, so it is unclear whether there is a truly superior dose, and the majority of trials have employed 7% HTS. Moreover, the percentage of HTS administered not only has implications for clinical efficacy, but also for patient adherence, since as doses increase (from 3% to 7%), so do nebulisation times, taste and tolerability, all important factors for compliance^[45]. A 1997 study by Robinson *et al.*^[25] showing increasing levels of sputum clearance with increasing concentrations of saline also noted that factors such as cough and oropharyngeal irritation increased in tandem with sputum clearance, and were highly disconcerting at concentrations approaching 12%, setting the ceiling of tolerability for the study. Tolerability is often a key determinant of the dose selected for an individual patient, with pre-treatment with bronchodilators aimed at facilitating a higher concentration. Roughly 5% of CF patients undergoing treatment with HTS will experience bronchospasm severe enough to restrict use^[8]. A commonly-used starting point for HTS is 7%, with bronchodilator pre-treatment, and with the willingness to down-titrate should patient comfort be sufficiently compromised. Administration of 7% HTS in conjunction with 0.1% hyaluronic acid *via* the aerosolised route has been shown to significantly improve tolerability and pleasantness when compared with 7% HTS alone^[46].

EFFECT OF HTS ON LEVELS OF AIRWAY INFLAMMATORY MEDIATORS INVOLVED IN NEUTROPHIL RECRUITMENT AND ACTIVATION

Circulating neutrophils are initially found in a resting state, and become primed upon exposure to chemo-

tactic stimuli comprising pathogenic molecules such as *N*-formyl peptides, cytokines including tumour necrosis factor- α (TNF- α) and chemokines including interleukin (IL)-8^[47]. The release of cytokines and chemokines including IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF) by CF epithelial cells functions to signal to circulating immune cells resulting in increased numbers of neutrophils and macrophages localized to the airways^[48,49]. IL-8 binds to the chemokine (C-X-C motif) receptor 1 (CXCR1) and CXCR2 on the plasma membrane of neutrophils resulting in cell adhesion^[50] and migration^[51]. In turn, synthesis and release of TNF- α and IL-1 β by recruited macrophages, and NE induced secretion of IL-8 and IL-6 by upper airway epithelial cells, perpetuate the cycle of inflammation^[52,53]. In addition, NE activity in BAL fluid is associated with early airways disease in children with CF^[54] and both NE and TNF- α up-regulate leukotriene B₄ (LTB₄) production by macrophages^[55,56], the latter a potent lipid inflammatory mediator. It has also been documented that CF lung epithelial cells release IL-8 in the absence of pathogens suggesting a persistent pro-inflammatory state (13, 14). Moreover, upon bacterial challenge studies have shown that the level of IL-8 released in response to infection is significantly increased in CF airway epithelial cells compared to CFTR sufficient cells and this has in part been explained by the plasma membrane surface expression of asialoganglioside 1 and toll-like receptor 4^[57,58].

Observations of increased cell migration and neutrophil-dominated chronic airway inflammation at an early age in children with CF^[59], supports the need for potential therapies that may target airway inflammatory mediators of neutrophil priming and migration. In this regard the ability of HTS to act as an anti-inflammatory, or alternatively pro-inflammatory agent, was studied by Chan *et al.*^[60]. IB3-1 bronchial epithelial cells containing the DF508/W1282X CF mutation were exposed to increasing concentrations of HTS *ex vivo* and secreted IL-8 levels were quantified. Results revealed that CFTR mutated bronchial epithelial cells produced an exaggerated level of both basal and NaCl-induced IL-8 production, indicating that HTS was acting as a pro-inflammatory stimuli^[60]. However, the highest concentration of HTS employed in this study was 125 mmol/L, which is in contrast to the therapeutic concentration of HTS used *in vivo* (513 mmol/L; 3%). Nevertheless, this effect of HTS was echoed by studies that demonstrated that hyperosmolar solutions stimulated cytokine production by bronchial epithelial cells *via* p38 mitogen-activated protein kinases activation^[61] and in CF bronchial gland cells *via* the NF- κ B pathway^[62]. Similarly, a study carried out by Shapiro *et al.*^[63] demonstrated that human peripheral blood mononuclear cells exposed to increasing concentrations of NaCl in combination with bacterial lipopolysaccharide or IL-1 exhibited increased protein expression of IL-8, IL-1 β and TNF- α .

HTS continues to be used as a therapy available

for the treatment of patients with CF^[64] and in contrast to the HTS-induced increased expression of IL-8 in *in vitro* studies, a number of *in vivo* studies have measured IL-8 levels following HTS treatment. These included a long term controlled trial of inhaled HTS in patients with CF, compared to inhaled isotonic saline, with no significant difference in sputum IL-8 levels found between the groups^[12]. Two further studies also investigated IL-8 levels in CF sputum post HTS (3% and 7%) nebulisation, with results showing no significant alteration in IL-8 levels^[65,66]. Moreover, an investigation designed to assess the effect of 7% HTS on airway inflammation in CF, with outcome measurements including altered IL-8, myeloperoxidase (MPO) and NE levels, revealed no increase in free IL-8 and the study did not support the capacity of HTS to promote inflammation in CF^[67]. Furthermore, in human pulmonary microvascular endothelial cells the ability of increasing concentrations of HTS (ranging from 140 mmol/L to 170 mmol/L NaCl) to significantly reduce TNF- α -induced IL-8 release was established^[68]. However, the concentration of HTS utilised was far below that used therapeutically. More recently, the functionality of HTS in reducing levels of IL-8 bound to glycosaminoglycans (GAGs) within the CF airways was observed. Within the CF airways, the dehydrated thick mucus contains raised levels of anionic GAGs formed on the surface of bronchial epithelial cell^[69], the most abundant including heparan sulphate (HS) and chondroitin sulphate (CS)^[70,71]. Of major importance, increased quantities of GAGs have been found in airway samples from individuals with CF^[72]. The immobilization of IL-8 by GAGs plays a major role in the establishment of gradients of the chemokine that contribute to the recruitment of neutrophils during inflammatory exacerbations^[73]. The use of an IL-8 decoy (PA401) with enhanced GAG binding ability^[74], or the removal of HS and CS lead to a significant reduction in the detection of this chemokine^[75]. Moreover, disruption of this interaction with increasing ionic concentrations (7% HTS) displaces IL-8 from GAGs, subjecting the former to clearance by proteolytic activity by NE^[76] (Figure 3). Although only a small number of patients were recruited to this latter study, and the effect of HTS on other immunomodulatory mediators in the CF airways was not evaluated, results are in line with the ability of aerosolized HTS in an animal model of acute lung injury to reduce levels of the murine analogue of IL-8, cytokine-induced neutrophil chemoattractant-1, by 44%^[77].

ABILITY OF HTS TO IMPACT UPON NEUTROPHIL ADHESION AND MIGRATION

Pro-inflammatory stimuli, either individually or in combination, can stimulate the neutrophil to change morphology and migrate to the airways, the latter being

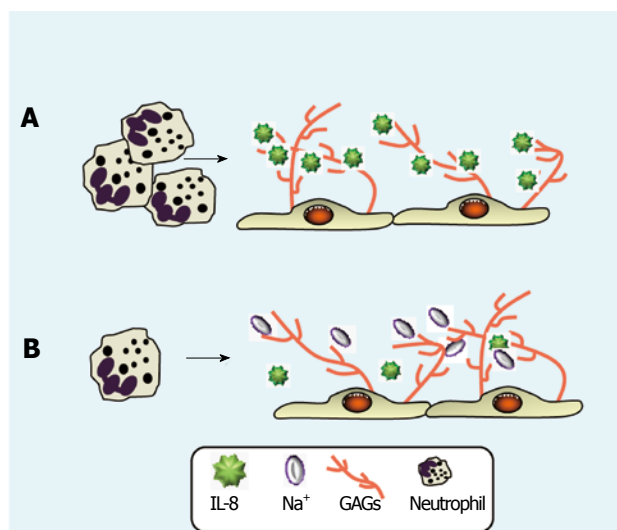


Figure 3 Hypertonic saline reduces levels of interleukin-8 in cystic fibrosis airway samples thereby reducing neutrophil migration. A: The chemokine IL-8 is a key mediator of inflammation in patients with CF and increases neutrophil migration to the airways. GAGs possess the ability to influence the chemokine profile of the CF lung by binding IL-8 and protecting it from proteolytic degradation; B: HTS functions to disrupt IL-8: GAG complexes, rendering the chemokine susceptible to proteolytic degradation. Clinical application of HTS may serve to decrease the inflammatory burden in the CF lung *in vivo*. CF: Cystic fibrosis; GAGs: Glycosaminoglycans; HTS: Hypertonic saline; IL-8: Interleukin-8.

a multistep process. Initially, after a chemotactic signal is received, the neutrophil reversibly binds to the vascular endothelium through the interactions between P-selectin and E-selectin found on the epithelium, with L-selectin expressed on the neutrophil surface. Rolling of neutrophils involves interaction between these selectins and glycoproteins such as P-selectin glycoprotein ligand (PSGL1) which is expressed by the endothelium and leukocytes. This mediated rolling of the cell allows new bonds to form before breaking of older bonds and shedding of L-selectin^[78]. This slow rolling then allows for tighter bonds to form between $\beta 2$ integrins expressed on the neutrophil surface including CD11b/CD18 and the corresponding ligands, intercellular adhesion molecule-1 (ICAM-1) and ICAM-2. Once neutrophils have adhered to the endothelial wall, tight junctions between endothelial cells become loose and allow transmigration. Neutrophils then follow a gradient of immobilised chemoattractants and travel to the airways along collagen and elastin fibres^[78] and movement through the extracellular matrix is facilitated by release of proteolytic enzymes including metalloproteases and NE^[79,80].

The capacity of HTS to reduce neutrophil migration as a result of lowering levels of the potent neutrophil chemoattractant IL-8 has been investigated. In this regard, the consequence of disruption of interactions between IL-8 and GAGs within the CF lung was addressed by assessing the chemotactic potency of sputum *ex vivo* following nebulized HTS treatment, with results demonstrating a reduction in

the neutrophil chemotactic index^[76]. Although IL-8 is a major chemotactic factor in CF, it is not the only chemoattractant found in the CF airways. Thus this latter study should be extended to evaluate the effect of HTS on additional chemoattractants including levels of formyl peptides, C5a^[81], and the more recently described chemotactic peptide, proline-glycine-proline^[82]. Nevertheless, in agreement with these latter findings, Aitken *et al.*^[65] showed that the percentage of neutrophils in liquefied sputum samples significantly decreased post HTS (3%) nebulization. Moreover, recent data indicates that HTS can inhibit platelet activating factor (PAF) stimulated cell adhesion. In this regard, exposure of neutrophils to PAF characteristically leads to increased CD11b/CD18 surface expression, and adhesion of PAF activated neutrophils was significantly inhibited by pretreatment with HTS, indicating that HTS may influence functional changes in neutrophils^[68]. This concept is further supported by a study demonstrating that HTS considerably reduced neutrophil chemotaxis in response to zymosan-activated serum^[83]. Moreover, HTS treatment decreased the number of neutrophils migrating to the airways in a rat model^[84], and has been shown to reduce neutrophil adhesion and rolling in a murine model^[85]. Although this latter study did not evaluate the neutrophil plasma membrane surface expression of either L-selectin or CD11b, diminished levels of both adhesion molecules in response to HTS had previously been documented^[86,87]. Moreover, while the use of animal models provides in-depth information on the efficacy of HTS usage, they are not representative of human disease and in particular the use of murine models in the study of CF is limited, as CF mice fail to develop spontaneous lung disease or chronic bacterial infection^[88].

IMPACT OF HTS ON NEUTROPHIL CELLULAR PROCESSES INCLUDING NADPH OXIDASE ACTIVITY AND DEGRANULATION

The process of neutrophil mediated bacterial clearance can be divided into two main procedures, those that are oxygen independent, and those that are oxygen dependent. These two cell processes are tightly regulated, and upon dysregulation, can result in release of reactive oxygen species and proteolytic enzymes to the surrounding lung tissues, as occurs in CF. Reactive oxygen species are produced by reduction of consumed oxygen. This reaction is catalysed by the NADPH oxidase, an enzyme complex that consists of two membrane proteins, p22^{phox} and gp91^{phox}, that constitute the heterodimeric flavoprotein cytochrome b₅₅₈, and four cytosolic components p67^{phox}, p47^{phox}, p40^{phox} and p21^{rac} (Figure 4). In the resting neutrophil the majority of membrane-associated flavoprotein cytochrome b₅₅₈ is localised to secondary granules

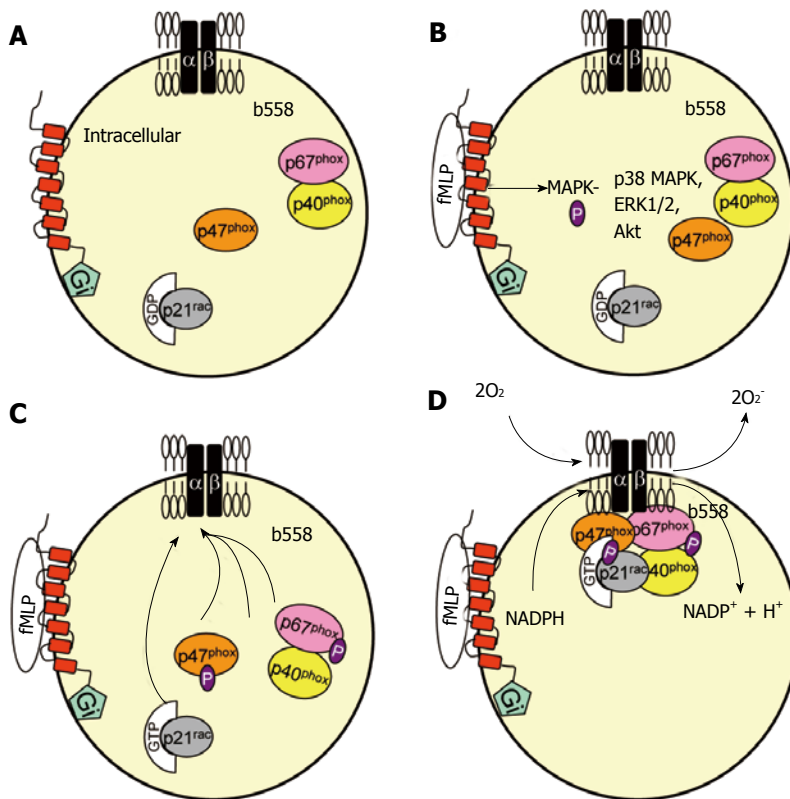


Figure 4 Schematic illustration of the NADPH oxidase of resting and formyl peptides activated cells. The neutrophil NADPH oxidase generates superoxide (O_2^-) and secondary oxygen-derived toxic products in response to bacteria or a variety of soluble stimuli (fMLP). A: The enzyme is dormant in resting neutrophils. The active site of this enzyme is located in an integral membrane cytochrome, b₅₅₈, which consists of the two subunits gp91^{phox} and p21^{phox} (subunits); B: Stimulation of the neutrophil by fMLP induces activation and phosphorylation (P) of a number of kinases including Akt; C: P21^{rac} is converted into the active GTP-bound form and the phosphorylation of the cytosolic components (p67^{phox}, p47^{phox} and p40^{phox}) occurs; D: These subunits then translocate to the membrane where they interact with cytochrome b₅₅₈ to initiate reactive oxygen species production. fMLP: Formyl peptides.

and the plasma membrane, whereas components p67^{phox}, p47^{phox} and p40^{phox} are localised within the cytosol together with GDP-bound p21^{rac}. Upon priming of the neutrophil with proinflammatory stimuli including fMLP or TNF-, partial assembly of the NADPH oxidase occurs involving phosphorylation of p67^{phox} and p47^{phox} followed by translocation to the flavocytochrome. The NADPH oxidase complex becomes fully assembled upon recruitment of GTP-bound p21^{rac}. Upon assembly, the active oxidase reduces NADPH and electrons are transferred *via* the flavocytochrome across the membrane to oxygen creating superoxide (O_2^-), which dismutates to hydrogen peroxide (H_2O_2). H_2O_2 generated during the oxidative burst has limited bactericidal properties and the best-defined function of H_2O_2 in the antimicrobial activities of neutrophils comes from the function of H_2O_2 as a substrate for MPO in the presence of halides [chloride (Cl^-)], resulting in the formation of hypochlorous acid (HOCl). HOCl is the most bactericidal oxidant known to be produced by neutrophils and as Dakin's solution, was extensively used in medicine in the treatment of topical wounds until antibiotics became available. Conversely, neutrophil-derived reactive oxygen species have been implicated in activation of NF- κ B, release of pro-inflammatory mediators, inhibition of apoptosis and recurring DNA damage^[89].

The second mechanism contributing to bacterial killing is mediated by enzymes stored in granules (Figure 5). Essential serine proteases stored in primary granules include NE, cathepsin G and proteinase 3. Each azurophilic granule contains 5.33 mmol/L NE, corresponding to approximately 67000 molecules per granule. NE, protease 3 and cathepsin G, are found in similar amounts and distribution in neutrophils^[90], however much of the research has focused on NE as it is the main mediator of proteolysis (Figure 6). As NE up-regulates expression of *other proteases* it has been suggested that neutralization of NE activity is central to reducing the overall protease burden within the airways^[91]. In addition, NE plays a central role in activation of matrix metalloproteinases (MMPs) which are synthesized in an inactive zymogen precursor form^[92]. For example, MMP-9 which exists as a pro-form, exhibits a molecular mass of 92 kDa which is cleaved by NE into an active molecule that is 72-kDa in size^[93]. In turn, increased levels of active MMP-9 can lead to the increased production of chemotactic peptides^[94] and extensive airway remodelling and inflammation^[95,96]. Thus, of the serine proteases, NE is the most harmful in the lung^[97] and it has been proposed as a target for therapeutic intervention in CF^[98,99]. Unopposed NE proteolytic action can degrade

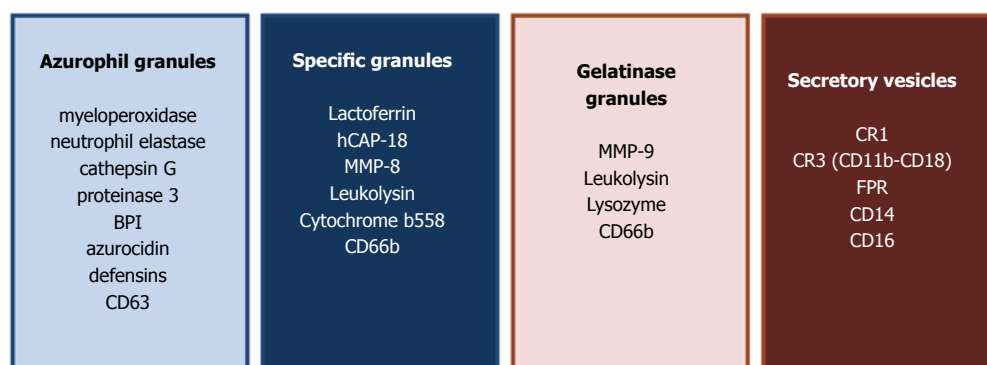


Figure 5 Components of neutrophil granules. The second mechanism of bacterial killing is mediated by enzymes stored in granules. Essential serine proteases stored in primary granules include NE, cathepsin G and proteinase 3. Other bactericidal proteins of primary granules include defensins, azurocidin and bactericidal permeability-increasing (BPI) protein, which mutually function to destabilise bacterial membranes. Additional antibacterial proteins stored in secondary or specific granules include lactoferrin, the 18-kDa human cathelicidin antimicrobial protein (hCAP18) and lysozyme. Lactoferrin, an iron binding protein displays antimicrobial properties by limiting iron availability and exhibits direct antimicrobial and antifungal properties independent of iron-binding. LL-37, the CX-terminal peptide of hCAP-18, disrupts the integrity of bacterial membranes and can neutralise bacterial endotoxins. The gelatinase or tertiary granules contain mainly gelatinase (MMP-9) whose main function is to degrade type V collagen in the extracellular matrix to aid neutrophil migration. In addition to these three granule types, neutrophils also contain secretory vesicles that contain a reservoir of essential receptors and integrins. All are degranulated to the outside of the cell or into the phagocytic vacuole.

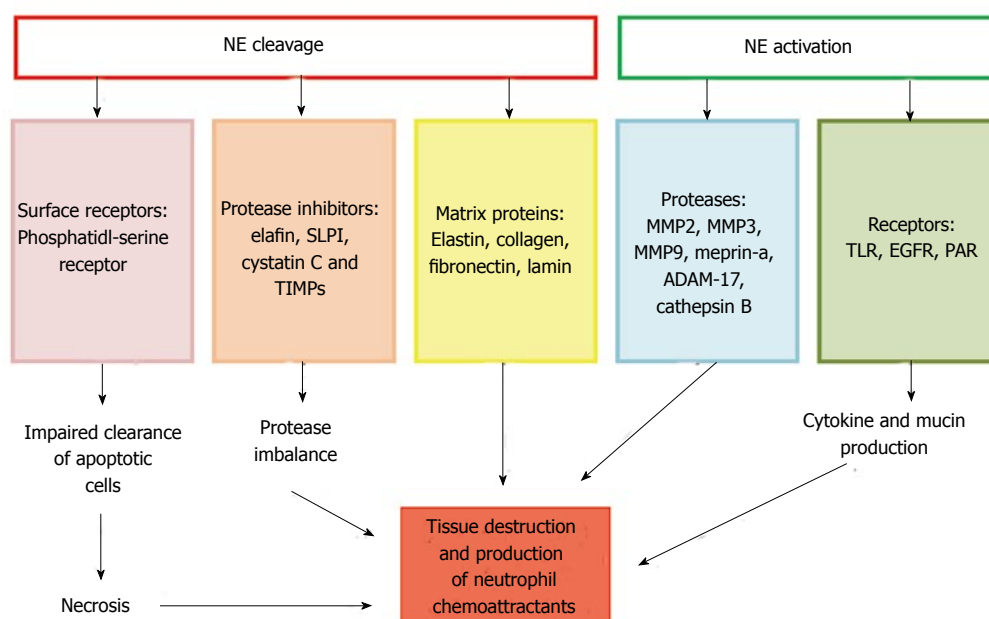


Figure 6 Potential effects of active neutrophil elastase in cystic fibrosis. Excessive NE activity can lead to proteolysis causing protease-antiprotease imbalance by cleaving protease inhibitors. Cleavage of matrix proteins and surface receptors leads to tissue damage and prolonged immune response, respectively. NE can further activate pro-inflammatory molecules (MMPs and ADAM-17) and receptors. These cumulative effects exacerbate tissue destruction and hyper-inflammation. NE: Neutrophil elastase; CF: Cystic fibrosis; MMPs: Matrix metalloproteinases.

molecules important in control of inflammation including receptors^[100], particularly those required for clearance of apoptotic neutrophils^[101] or bacterial phagocytosis^[102,103]. NE can also inactivate and degrade antiproteases including elafin^[104], alpha-1 antitrypsin and secretory leukocyte inhibitor^[105]. As a consequence of the proteases/antiprotease imbalance, lung tissue is irreversibly damaged, dramatically reducing lung function and ultimately causing respiratory failure^[106]. In short, HTS therapies that may modulate exuberant oxidase and degranulation activity may be used as powerful anti-inflammatories within the setting of CF

airways disease.

A number of *in vitro* investigations have documented that sodium chloride slows neutrophil activity^[107] and a study evaluating the effect of HTS on the mechanisms of activation of the NADPH oxidase revealed that stimulated translocation of p67^{phox} to the neutrophil membrane in response to PAF was prevented. Moreover, in *in vitro* cell-free oxidase assays, the membrane content of p67^{phox} post PAF activation was increased in support of oxidase activity, whereas control unstimulated and HTS-PAF activated membranes contained equivalent p67^{phox} protein content^[108]. Although these results

support the potential of HTS to modulate oxidase activity, the concentration of HTS utilised was 180 mmol/L, which is below therapeutic HTS and therefore higher concentrations of HTS should be investigated to determine the effect on p67^{phox} membrane translocation. Nevertheless, the inhibitory effect of HTS on a second stimuli involving fMLP-induced NADPH oxidase was also confirmed. The described inhibition occurred in a dose-dependent manner with results indicating that transient increases in osmolality caused prolonged suppression of neutrophil O₂⁻ production to the outside of the cell, as measured by cytochrome c reduction^[83]. The mechanism of inhibition was explored and shown to involve blockade of mitogen activated protein kinase (MAPK) ERK 1/2 and p38 signalling^[83]. Moreover, H₂O₂ production to the outside of the cell post fMLP activation was equally reduced by two concentrations of HTS ([Na⁺] = 180 mmol/L and 200 mmol/L)^[109]. In contrast however, and of major importance, intracellular formation of reactive oxygen species upon bacterial phagocytosis was potentiated with increasing osmolar strength^[110]. Despite osmotic down-regulation of p38 and ERK-1, this later study demonstrated enhanced intracellular O₂⁻ generation in response to bacterial challenge suggesting that HTS may attenuate tissue injury by compromising neutrophil cytotoxic capacity, and additionally appears to enhance the response to bacteria. This may be a further beneficial role of HTS when aerosolized clinically in CF^[110].

With respect to the ability of HTS to modulate the degranulation process, Junger *et al.*^[83] demonstrated that neutrophils exposed to > 50 mmol/L HTS alone released increased levels of MPO and NE, however, when cells were exposed simultaneously to inflammatory levels of fMLP and increasing concentrations of HTS, as would be expected in the CF airways, the fMLP-stimulated primary granule release of MPO^[20] and NE was inhibited in a dose dependent manner. Moreover, HTS induced changes in the actin cytoskeleton have been reported^[111] and linked to the hypertonic inhibition of neutrophil degranulation. HTS instigated a twofold increase in F-actin formation and abrogated the mobilization of all granule types suggesting cytoskeletal remodelling as a key component in the neutrophil-suppressive anti-inflammatory effects of HTS^[112]. As neutrophils in individuals with CF demonstrate enhanced secretion of NE and MPO, the potential of aerosolized HTS to prevent primary granule release would have tremendous clinical implications. Furthermore, despite the fact that there is abundant extracellular neutrophil released hCAP-18/LL-37 in the lungs of individuals with CF, the lung fluid from patients exhibits poor antimicrobial activity. A recent study has demonstrated that the antimicrobial activity of endogenous hCAP-18/LL-37 in CF BAL fluid is rendered inactive by binding GAGs but is liberated following nebulized HTS^[113]. The effect of HTS on levels of additional antimicrobial peptides and proteins within the CF airways was not evaluated but this study does suggest that a strategy

whereby nebulized HTS augments antimicrobial activity may provide optimization of the innate antimicrobial activity in the setting of CF.

CONCLUSION

HTS treatment is associated with an improvement in lung function and marked benefits with respect to exacerbations^[26,114,115]. Significant inflammation in the airways manifests from a very young age in CF most likely due to a combination of intrinsic innate immune dysregulation and infection. The obvious most effective treatment remains correction of CFTR dysfunction at a very early age, thereby curtailing development of airway inflammation. However, in the absence of CFTR ion channel modulators for each individual's genotype it will remain important to modulate or suppress the inflammatory reactions of the disease. Although in children with CF, the use of inhaled HTS did not reduce the rate of pulmonary exacerbations^[116], the described studies in the present review demonstrate dramatic *in vitro* effects of HTS on neutrophil function, limiting cellular processes that govern airway inflammation including cell adhesion, reactive oxygen species production and protease release. These reports support the concept that HTS may have beneficial anti-inflammatory effects other than simply increasing mucociliary clearance and thus further investigations of the potential mechanisms of this currently available therapy in CF is crucially required.

REFERENCES

- 1 **Burns JL**, Emerson J, Stapp JR, Yim DL, Krzewinski J, Loudon L, Ramsey BW, Clausen CR. Microbiology of sputum from patients at cystic fibrosis centers in the United States. *Clin Infect Dis* 1998; **27**: 158-163 [PMID: 9675470 DOI: 10.1086/514631]
- 2 **Wood RE**, Boat TF, Doershuk CF. Cystic fibrosis. *Am Rev Respir Dis* 1976; **113**: 833-878 [PMID: 779549]
- 3 **De Boeck K**, Zolin A, Cuppens H, Olesen HV, Viviani L. The relative frequency of CFTR mutation classes in European patients with cystic fibrosis. *J Cyst Fibros* 2014; **13**: 403-409 [PMID: 24440181 DOI: 10.1016/j.jcf.2013.12.003]
- 4 **Zielenski J**, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. *Annu Rev Genet* 1995; **29**: 777-807 [PMID: 8825494 DOI: 10.1146/annurev.ge.29.120195.004021]
- 5 **Boucher RC**, Stutts MJ, Knowles MR, Cantley L, Gatzky JT. Na⁺ transport in cystic fibrosis respiratory epithelia. Abnormal basal rate and response to adenylate cyclase activation. *J Clin Invest* 1986; **78**: 1245-1252 [PMID: 3771796 DOI: 10.1172/JCI112708]
- 6 **Stutts MJ**, Canessa CM, Olsen JC, Hamrick M, Cohn JA, Rossier BC, Boucher RC. CFTR as a cAMP-dependent regulator of sodium channels. *Science* 1995; **269**: 847-850 [PMID: 7543698 DOI: 10.1126/science.7543698]
- 7 **Matsui H**, Grubb BR, Tarran R, Randell SH, Gatzky JT, Davis CW, Boucher RC. Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. *Cell* 1998; **95**: 1005-1015 [PMID: 9875854 DOI: 10.1016/S0092-8674(00)81724-9]
- 8 **Boucher RC**. Evidence for airway surface dehydration as the initiating event in CF airway disease. *J Intern Med* 2007; **261**: 5-16 [PMID: 17222164 DOI: 10.1111/j.1365-2796.2006.01744.x]
- 9 **McCarthy C**, Dimitrov BD, Meurling IJ, Gunaratnam C, McElvaney NG. The CF-ABLE score: a novel clinical prediction

- rule for prognosis in patients with cystic fibrosis. *Chest* 2013; **143**: 1358-1364 [PMID: 23172242 DOI: 10.1378/chest.12-2022]
- 10 **O'Sullivan BP**, Flume P. The clinical approach to lung disease in patients with cystic fibrosis. *Semin Respir Crit Care Med* 2009; **30**: 505-513 [PMID: 19760538 DOI: 10.1055/s-0029-1238909]
 - 11 **Eng PA**, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol* 1996; **21**: 77-83 [PMID: 8882210]
 - 12 **Elkins MR**, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, Xuan W, Bye PT. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006; **354**: 229-240 [PMID: 16421364 DOI: 10.1056/NEJMoa04390]
 - 13 **Hardt D**, Griese M, Kappler M, Zissel G, Reinhardt D, Rebhan C, Schendel DJ, Krauss-Etschmann S. Pulmonary T(H)2 response in *Pseudomonas aeruginosa*-infected patients with cystic fibrosis. *J Allergy Clin Immunol* 2006; **117**: 204-211 [PMID: 16387607 DOI: 10.1016/j.jaci.2005.09.023]
 - 14 **Birrer P**, McElvaney NG, Rüdeberg A, Sommer CW, Liechti-Gallati S, Kraemer R, Hubbard R, Crystal RG. Protease-antiprotease imbalance in the lungs of children with cystic fibrosis. *Am J Respir Crit Care Med* 1994; **150**: 207-213 [PMID: 7912987 DOI: 10.1164/ajrccm.150.1.7912987]
 - 15 **McElvaney NG**, Nakamura H, Birrer P, Hébert CA, Wong WL, Alphonso M, Baker JB, Catalano MA, Crystal RG. Modulation of airway inflammation in cystic fibrosis. In vivo suppression of interleukin-8 levels on the respiratory epithelial surface by aerosolization of recombinant secretory leukoprotease inhibitor. *J Clin Invest* 1992; **90**: 1296-1301 [PMID: 1357002 DOI: 10.1172/JCI115994]
 - 16 **Di A**, Brown ME, Deriy LV, Li C, Szeto FL, Chen Y, Huang P, Tong J, Naren AP, Bindokas V, Palfrey HC, Nelson DJ. CFTR regulates phagosome acidification in macrophages and alters bactericidal activity. *Nat Cell Biol* 2006; **8**: 933-944 [PMID: 16921366 DOI: 10.1038/ncb1456]
 - 17 **Morris MR**, Doull IJ, Dewitt S, Hallett MB. Reduced iC3b-mediated phagocytotic capacity of pulmonary neutrophils in cystic fibrosis. *Clin Exp Immunol* 2005; **142**: 68-75 [PMID: 16178858 DOI: 10.1111/j.1365-2249.2005.02893.x]
 - 18 **Painter RG**, Valentine VG, Lanson NA, Leidal K, Zhang Q, Lombard G, Thompson C, Viswanathan A, Nauseef WM, Wang G, Wang G. CFTR Expression in human neutrophils and the phagolysosomal chlorination defect in cystic fibrosis. *Biochemistry* 2006; **45**: 10260-10269 [PMID: 16922501 DOI: 10.1021/bi060490t]
 - 19 **Yoshimura K**, Nakamura H, Trapnell BC, Chu CS, Dalemans W, Pavirani A, Lecocq JP, Crystal RG. Expression of the cystic fibrosis transmembrane conductance regulator gene in cells of non-epithelial origin. *Nucleic Acids Res* 1991; **19**: 5417-5423 [PMID: 1717947 DOI: 10.1093/nar/19.19.5417]
 - 20 **Pohl K**, Hayes E, Keenan J, Henry M, Meleady P, Molloy K, Jundi B, Bergin DA, McCarthy C, McElvaney OJ, White MM, Clynes M, Reeves EP, McElvaney NG. A neutrophil intrinsic impairment affecting Rab27a and degranulation in cystic fibrosis is corrected by CFTR potentiator therapy. *Blood* 2014; **124**: 999-1009 [PMID: 24934256 DOI: 10.1182/blood-2014-02-555268]
 - 21 **Ng HP**, Zhou Y, Song K, Hodges CA, Drumm ML, Wang G. Neutrophil-mediated phagocytic host defense defect in myeloid Cfr-inactivated mice. *PLoS One* 2014; **9**: e106813 [PMID: 25184794 DOI: 10.1371/journal.pone.0106813]
 - 22 **Tirouvanziam R**, Gernez Y, Conrad CK, Moss RB, Schrijver I, Dunn CE, Davies ZA, Herzenberg LA, Herzenberg LA. Profound functional and signaling changes in viable inflammatory neutrophils homing to cystic fibrosis airways. *Proc Natl Acad Sci USA* 2008; **105**: 4335-4339 [PMID: 18334635]
 - 23 **Makam M**, Diaz D, Laval J, Gernez Y, Conrad CK, Dunn CE, Davies ZA, Moss RB, Herzenberg LA, Herzenberg LA, Tirouvanziam R. Activation of critical, host-induced, metabolic and stress pathways marks neutrophil entry into cystic fibrosis lungs. *Proc Natl Acad Sci USA* 2009; **106**: 5779-5783 [PMID: 19293384 DOI: 10.1073/pnas.0813410106]
 - 24 **Laval J**, Touhami J, Herzenberg LA, Conrad C, Taylor N, Battini JL, Sitbon M, Tirouvanziam R. Metabolic adaptation of neutrophils in cystic fibrosis airways involves distinct shifts in nutrient transporter expression. *J Immunol* 2013; **190**: 6043-6050 [PMID: 23690474 DOI: 10.4049/jimmunol.1201755]
 - 25 **Robinson M**, Hemming AL, Regnis JA, Wong AG, Bailey DL, Bautovich GJ, King M, Bye PT. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. *Thorax* 1997; **52**: 900-903 [PMID: 9404379 DOI: 10.1136/thx.52.10.900]
 - 26 **Donaldson SH**, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med* 2006; **354**: 241-250 [PMID: 16421365 DOI: 10.1056/NEJMoa043891]
 - 27 **Robinson M**, Regnis JA, Bailey DL, King M, Bautovich GJ, Bye PT. Effect of hypertonic saline, amiloride, and cough on mucociliary clearance in patients with cystic fibrosis. *Am J Respir Crit Care Med* 1996; **153**: 1503-1509 [PMID: 8630593 DOI: 10.1164/ajrccm.153.5.8630593]
 - 28 **Ballmann M**, von der Hardt H. Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis. *J Cyst Fibros* 2002; **1**: 35-37 [PMID: 15463808 DOI: 10.1016/S1569-1993(01)00009-1]
 - 29 **Dmello D**, Nayak RP, Matuschak GM. Stratified assessment of the role of inhaled hypertonic saline in reducing cystic fibrosis pulmonary exacerbations: a retrospective analysis. *BMJ Open* 2011; **1**: e000019 [PMID: 22021727 DOI: 10.1136/bmjopen-2010-000019]
 - 30 **Dentice R**, Elkins M, Bye P. A randomized trial of hypertonic saline nebulisation during hospitalisation for pulmonary exacerbation in adults with cystic fibrosis. *Pediatr Pulmonol* 2012; **47**: 257 [DOI: 10.1002/ppul.22682]
 - 31 **Wark P**, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* 2009; **(2)**: CD001506 [PMID: 19370568 DOI: 10.1002/14651858.CD001506.pub3]
 - 32 **Gustafsson PM**, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J* 2003; **22**: 972-979 [PMID: 14680088 DOI: 10.1183/09031936.03.00049502]
 - 33 **Aurora P**, Stanojevic S, Wade A, Oliver C, Kozłowska W, Lum S, Bush A, Price J, Carr SB, Shankar A, Stocks J. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2011; **183**: 752-758 [PMID: 20935113 DOI: 10.1164/rccm.200911-1646OC]
 - 34 **Ellemunter H**, Fuchs SI, Unsinn KM, Freund MC, Waltner-Romen M, Steinkamp G, Gappa M. Sensitivity of Lung Clearance Index and chest computed tomography in early CF lung disease. *Respir Med* 2010; **104**: 1834-1842 [PMID: 20637585 DOI: 10.1016/j.rmed.2010.06.010]
 - 35 **Gustafsson PM**, De Jong PA, Tiddens HA, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. *Thorax* 2008; **63**: 129-134 [PMID: 17675316 DOI: 10.1136/thx.2007.077784]
 - 36 **Amin R**, Subbarao P, Jabar A, Balkovec S, Jensen R, Kerrigan S, Gustafsson P, Ratjen F. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. *Thorax* 2010; **65**: 379-383 [PMID: 20435858 DOI: 10.1136/thx.2009.125831]
 - 37 **Dellon EP**, Donaldson SH, Johnson R, Davis SD. Safety and tolerability of inhaled hypertonic saline in young children with cystic fibrosis. *Pediatr Pulmonol* 2008; **43**: 1100-1106 [PMID: 18828160 DOI: 10.1002/ppul.20909]
 - 38 **Rosenfeld M**, Davis S, Brumback L, Daniel S, Rowbotham R, Johnson R, McNamara S, Jensen R, Barlow C, Ratjen F. Inhaled hypertonic saline in infants and toddlers with cystic fibrosis: short-term tolerability, adherence, and safety. *Pediatr Pulmonol* 2011; **46**: 666-671 [PMID: 21365779 DOI: 10.1002/ppul.21425]
 - 39 **Subbarao P**, Balkovec S, Solomon M, Ratjen F. Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis. *Pediatr Pulmonol* 2007; **42**: 471-476 [PMID: 17436328 DOI: 10.1002/ppul.20603]
 - 40 **Laube BL**, Sharpless G, Carson KA, Kelly A, Mogayzel PJ. Acute

- inhalation of hypertonic saline does not improve mucociliary clearance in all children with cystic fibrosis. *BMC Pulm Med* 2011; **11**: 45 [PMID: 21896198 DOI: 10.1186/1471-2466-11-45]
- 41 **Donaldson SD**, LaFave C, Wu J, Zeman K, Salazar C, Bennett WD, Davis SD. Sustained effect of hypertonic saline on mucociliary clearance in CF children with mild lung disease. *Pediatr Pulmonol* 2013; **48**: 71-102 [DOI: 10.1002/ppul.22897]
 - 42 **Havasi V**, Hurst CO, Briles TC, Yang F, Bains DG, Hassett DJ, Sorscher E. Inhibitory effects of hypertonic saline on *P. aeruginosa* motility. *J Cyst Fibros* 2008; **7**: 267-269 [PMID: 18249160 DOI: 10.1016/j.jcf.2007.11.009]
 - 43 **Anderson GG**, O'Toole GA. Innate and induced resistance mechanisms of bacterial biofilms. *Curr Top Microbiol Immunol* 2008; **322**: 85-105 [PMID: 18453273 DOI: 10.1007/978-3-540-75418-3_5]
 - 44 **Gupta S**, Ahmed F, Lodha R, Gupta YK, Kabra SK. Comparison of effects of 3 and 7% hypertonic saline nebulization on lung function in children with cystic fibrosis: a double-blind randomized, controlled trial. *J Trop Pediatr* 2012; **58**: 375-381 [PMID: 22374985 DOI: 10.1093/tropej/fms004]
 - 45 **Enderby B**, Doull I. Hypertonic saline inhalation in cystic fibrosis-salt in the wound, or sweet success? *Arch Dis Child* 2007; **92**: 195-196 [PMID: 17337677 DOI: 10.1136/adc.2006.094979]
 - 46 **Buonpensiero P**, De Gregorio F, Sepe A, Di Pasqua A, Ferri P, Siano M, Terlizzi V, Raia V. Hyaluronic acid improves "pleasantness" and tolerability of nebulized hypertonic saline in a cohort of patients with cystic fibrosis. *Adv Ther* 2010; **27**: 870-878 [PMID: 20953746 DOI: 10.1007/s12325-010-0076-8]
 - 47 **Mantovani A**, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol* 2011; **11**: 519-531 [PMID: 21785456 DOI: 10.1038/nri3024]
 - 48 **Becker MN**, Sauer MS, Muhlebach MS, Hirsh AJ, Wu Q, Verghese MW, Randell SH. Cytokine secretion by cystic fibrosis airway epithelial cells. *Am J Respir Crit Care Med* 2004; **169**: 645-653 [PMID: 14670800 DOI: 10.1164/rccm.200207-765OC]
 - 49 **Perez A**, Issler AC, Cotton CU, Kelley TJ, Verkman AS, Davis PB. CFTR inhibition mimics the cystic fibrosis inflammatory profile. *Am J Physiol Lung Cell Mol Physiol* 2007; **292**: L383-L395 [PMID: 16920886]
 - 50 **Takami M**, Terry V, Petruzzelli L. Signaling pathways involved in IL-8-dependent activation of adhesion through Mac-1. *J Immunol* 2002; **168**: 4559-4566 [PMID: 11971003 DOI: 10.4049/jimmunol.168.9.4559]
 - 51 **Hammond ME**, Lapointe GR, Feucht PH, Hilt S, Gallegos CA, Gordon CA, Giedlin MA, Mullenbach G, Tekamp-Olson P. IL-8 induces neutrophil chemotaxis predominantly via type I IL-8 receptors. *J Immunol* 1995; **155**: 1428-1433 [PMID: 7636208]
 - 52 **Bédard M**, McClure CD, Schiller NL, Francoeur C, Cantin A, Denis M. Release of interleukin-8, interleukin-6, and colony-stimulating factors by upper airway epithelial cells: implications for cystic fibrosis. *Am J Respir Cell Mol Biol* 1993; **9**: 455-462 [PMID: 7691110 DOI: 10.1165/ajrcmb/9.4.455]
 - 53 **Ruef C**, Jefferson DM, Schlegel-Haueter SE, Suter S. Regulation of cytokine secretion by cystic fibrosis airway epithelial cells. *Eur Respir J* 1993; **6**: 1429-1436 [PMID: 8112434]
 - 54 **Sly PD**, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* 2013; **368**: 1963-1970 [PMID: 23692169 DOI: 10.1056/NEJMoa1301725]
 - 55 **Greally P**, Hussein MJ, Cook AJ, Sampson AP, Piper PJ, Price JF. Sputum tumour necrosis factor-alpha and leukotriene concentrations in cystic fibrosis. *Arch Dis Child* 1993; **68**: 389-392 [PMID: 8385438]
 - 56 **Hubbard RC**, Fells G, Gadek J, Pacholok S, Humes J, Crystal RG. Neutrophil accumulation in the lung in alpha 1-antitrypsin deficiency. Spontaneous release of leukotriene B4 by alveolar macrophages. *J Clin Invest* 1991; **88**: 891-897 [PMID: 1653278 DOI: 10.1172/JCI115391]
 - 57 **Greene CM**, Carroll TP, Smith SG, Taggart CC, Devaney J, Griffin S, O'Neill SJ, McElvaney NG. TLR-induced inflammation in cystic fibrosis and non-cystic fibrosis airway epithelial cells. *J Immunol* 2005; **174**: 1638-1646 [PMID: 15661927 DOI: 10.4049/jimmunol.174.3.1638]
 - 58 **Saiman L**, Prince A. *Pseudomonas aeruginosa* pili bind to asialoGM1 which is increased on the surface of cystic fibrosis epithelial cells. *J Clin Invest* 1993; **92**: 1875-1880 [PMID: 8104958 DOI: 10.1172/JCI116779]
 - 59 **Balough K**, McCubbin M, Weinberger M, Smits W, Ahrens R, Fick R. The relationship between infection and inflammation in the early stages of lung disease from cystic fibrosis. *Pediatr Pulmonol* 1995; **20**: 63-70 [PMID: 8570304 DOI: 10.1002/ppul.1950200203]
 - 60 **Chan MM**, Chmura K, Chan ED. Increased NaCl-induced interleukin-8 production by human bronchial epithelial cells is enhanced by the DeltaF508/W1282X mutation of the cystic fibrosis transmembrane conductance regulator gene. *Cytokine* 2006; **33**: 309-316 [PMID: 16647268 DOI: 10.1016/j.cyt.2006.03.003]
 - 61 **Hashimoto S**, Matsumoto K, Gon Y, Nakayama T, Takeshita I, Horie T. Hyperosmolarity-induced interleukin-8 expression in human bronchial epithelial cells through p38 mitogen-activated protein kinase. *Am J Respir Crit Care Med* 1999; **159**: 634-640 [PMID: 9927384 DOI: 10.1164/ajrcm.159.2.9712090]
 - 62 **Tabary O**, Escotte S, Couetil JP, Hubert D, Dusser D, Puchelle E, Jacquot J. High susceptibility for cystic fibrosis human airway gland cells to produce IL-8 through the I kappa B kinase alpha pathway in response to extracellular NaCl content. *J Immunol* 2000; **164**: 3377-3384 [PMID: 10706733]
 - 63 **Shapiro L**, Dinarello CA. Hyperosmotic stress as a stimulant for proinflammatory cytokine production. *Exp Cell Res* 1997; **231**: 354-362 [PMID: 9087177 DOI: 10.1006/excr.1997.3476]
 - 64 **Goss CH**, Ratjen F. Update in cystic fibrosis 2012. *Am J Respir Crit Care Med* 2013; **187**: 915-919 [PMID: 23634859 DOI: 10.1164/rccm.201301-0184UP]
 - 65 **Aitken ML**, Greene KE, Tonelli MR, Burns JL, Emerson JC, Goss CH, Gibson RL. Analysis of sequential aliquots of hypertonic saline solution-induced sputum from clinically stable patients with cystic fibrosis. *Chest* 2003; **123**: 792-799 [PMID: 12628880 DOI: 10.1378/chest.123.3.792]
 - 66 **Suri R**, Metcalfe C, Lees B, Grieve R, Flather M, Normand C, Thompson S, Bush A, Wallis C. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. *Lancet* 2001; **358**: 1316-1321 [PMID: 11684212 DOI: 10.1016/S0140-6736(01)06412-1]
 - 67 **Suri R**, Marshall LJ, Wallis C, Metcalfe C, Bush A, Shute JK. Effects of recombinant human DNase and hypertonic saline on airway inflammation in children with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **166**: 352-355 [PMID: 12153969 DOI: 10.1164/rccm.2110015]
 - 68 **Banerjee A**, Moore EE, McLaughlin NJ, Lee L, Jones WL, Johnson JL, Nydam TL, Silliman CC. Hyperosmolarity attenuates TNF- α -mediated proinflammatory activation of human pulmonary microvascular endothelial cells. *Shock* 2013; **39**: 366-372 [PMID: 23364439 DOI: 10.1097/SHK.0b013e3182894016]
 - 69 **Reeves EP**, Bergin DA, Murray MA, McElvaney NG. The involvement of glycosaminoglycans in airway disease associated with cystic fibrosis. *ScientificWorldJournal* 2011; **11**: 959-971 [PMID: 21516290 DOI: 10.1100/tsw.2011.81]
 - 70 **Solic N**, Wilson J, Wilson SJ, Shute JK. Endothelial activation and increased heparan sulfate expression in cystic fibrosis. *Am J Respir Crit Care Med* 2005; **172**: 892-898 [PMID: 15976375 DOI: 10.1164/rccm.200409-1207OC]
 - 71 **Suki B**, Ito S, Stamenovic D, Lutchen KR, Ingenito EP. Biomechanics of the lung parenchyma: critical roles of collagen and mechanical forces. *J Appl Physiol* (1985) 2005; **98**: 1892-1899 [PMID: 15829722 DOI: 10.1152/japplphysiol.01087.2004]
 - 72 **Hilliard TN**, Regamey N, Shute JK, Nicholson AG, Alton EW, Bush A, Davies JC. Airway remodelling in children with cystic fibrosis. *Thorax* 2007; **62**: 1074-1080 [PMID: 17526676 DOI: 10.1136/thx.2006.074641]
 - 73 **Proudfoot AE**, Handel TM, Johnson Z, Lau EK, LiWang P, Clark-Lewis I, Borlat F, Wells TN, Kosco-Vilbois MH.

- Glycosaminoglycan binding and oligomerization are essential for the in vivo activity of certain chemokines. *Proc Natl Acad Sci USA* 2003; **100**: 1885-1890 [PMID: 12571364 DOI: 10.1073/pnas.0334864100]
- 74 **McElvaney OJ**, O'Reilly N, White M, Lacey N, Pohl K, Gerlza T, Bergin DA, Kerr H, McCarthy C, O'Brien ME, Adage T, Kungl AJ, Reeves EP, McElvaney NG. The effect of the decoy molecule PA401 on CXCL8 levels in bronchoalveolar lavage fluid of patients with cystic fibrosis. *Mol Immunol* 2015; **63**: 550-558 [PMID: 25453468 DOI: 10.1016/j.molimm.2014.10.013]
- 75 **Frevert CW**, Kinsella MG, Vathanaprida C, Goodman RB, Baskin DG, Proudfoot A, Wells TN, Wight TN, Martin TR. Binding of interleukin-8 to heparan sulfate and chondroitin sulfate in lung tissue. *Am J Respir Cell Mol Biol* 2003; **28**: 464-472 [PMID: 12654635 DOI: 10.1165/rccm.2002-0084OC]
- 76 **Reeves EP**, Williamson M, O'Neill SJ, Grealley P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis. *Am J Respir Crit Care Med* 2011; **183**: 1517-1523 [PMID: 21330456 DOI: 10.1164/rccm.201101-0072OC]
- 77 **Wohlaue M**, Moore EE, Silliman CC, Fragoso M, Gamboni F, Harr J, Accurso F, Wright F, Haenel J, Fullerton D, Banerjee A. Nebulized hypertonic saline attenuates acute lung injury following trauma and hemorrhagic shock via inhibition of matrix metalloproteinase-13. *Crit Care Med* 2012; **40**: 2647-2653 [PMID: 22732292 DOI: 10.1097/CCM.0b013e3182592006]
- 78 **Mandeville JT**, Lawson MA, Maxfield FR. Dynamic imaging of neutrophil migration in three dimensions: mechanical interactions between cells and matrix. *J Leukoc Biol* 1997; **61**: 188-200 [PMID: 9021925]
- 79 **Delclaux C**, Delacourt C, D'Ortho MP, Boyer V, Lafuma C, Harf A. Role of gelatinase B and elastase in human polymorphonuclear neutrophil migration across basement membrane. *Am J Respir Cell Mol Biol* 1996; **14**: 288-295 [PMID: 8845180 DOI: 10.1165/ajrcmb.14.3.8845180]
- 80 **Lin M**, Jackson P, Tester AM, Diaconu E, Overall CM, Blalock JE, Pearlman E. Matrix metalloproteinase-8 facilitates neutrophil migration through the corneal stromal matrix by collagen degradation and production of the chemotactic peptide Pro-Gly-Pro. *Am J Pathol* 2008; **173**: 144-153 [PMID: 18556780 DOI: 10.2353/ajpath.2008.080081]
- 81 **Mackerness KJ**, Jenkins GR, Bush A, Jose PJ. Characterisation of the range of neutrophil stimulating mediators in cystic fibrosis sputum. *Thorax* 2008; **63**: 614-620 [PMID: 18245144 DOI: 10.1136/thx.2007.089359]
- 82 **Gaggar A**, Jackson PL, Noerager BD, O'Reilly PJ, McQuaid DB, Rowe SM, Clancy JP, Blalock JE. A novel proteolytic cascade generates an extracellular matrix-derived chemoattractant in chronic neutrophilic inflammation. *J Immunol* 2008; **180**: 5662-5669 [PMID: 18390751]
- 83 **Junger WG**, Hoyt DB, Davis RE, Herdon-Remelius C, Namiki S, Junger H, Loomis W, Altman A. Hypertonicity regulates the function of human neutrophils by modulating chemoattractant receptor signaling and activating mitogen-activated protein kinase p38. *J Clin Invest* 1998; **101**: 2768-2779 [PMID: 9637711 DOI: 10.1172/JCI1354]
- 84 **Rizoli SB**, Kapus A, Fan J, Li YH, Marshall JC, Rotstein OD. Immunomodulatory effects of hypertonic resuscitation on the development of lung inflammation following hemorrhagic shock. *J Immunol* 1998; **161**: 6288-6296 [PMID: 9834118]
- 85 **Pascual JL**, Ferri LE, Seely AJ, Campisi G, Chaudhury P, Giannias B, Evans DC, Razeq T, Michel RP, Christou NV. Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage. *Ann Surg* 2002; **236**: 634-642 [PMID: 12409670 DOI: 10.1097/01.SLA.0000032941.57077.A2]
- 86 **Angle N**, Hoyt DB, Coimbra R, Liu F, Herdon-Remelius C, Loomis W, Junger WG. Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock* 1998; **9**: 164-170 [PMID: 9525322 DOI: 10.1097/00024382-199803000-00002]
- 87 **Ciesla DJ**, Moore EE, Zallen G, Biffl WL, Silliman CC. Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: timing is everything. *J Trauma* 2000; **48**: 388-395 [PMID: 10744274 DOI: 10.1097/00005373-200003000-00004]
- 88 **Fisher JT**, Zhang Y, Engelhardt JF. Comparative biology of cystic fibrosis animal models. *Methods Mol Biol* 2011; **742**: 311-334 [PMID: 21547741 DOI: 10.1007/978-1-61779-120-8_19]
- 89 **Yao H**, Yang SR, Kode A, Rajendrasozhan S, Caito S, Adenuga D, Henry R, Edirisinghe I, Rahman I. Redox regulation of lung inflammation: role of NADPH oxidase and NF-kappaB signalling. *Biochem Soc Trans* 2007; **35**: 1151-1155 [PMID: 17956299 DOI: 10.1042/BST0351151]
- 90 **Campbell EJ**, Campbell MA, Owen CA. Bioactive proteinase 3 on the cell surface of human neutrophils: quantification, catalytic activity, and susceptibility to inhibition. *J Immunol* 2000; **165**: 3366-3374 [PMID: 10975855]
- 91 **Geraghty P**, Rogan MP, Greene CM, Boxio RM, Poiriert T, O' Mahony M, Belaouaj A, O'Neill SJ, Taggart CC, McElvaney NG. Neutrophil elastase up-regulates cathepsin B and matrix metalloproteinase-2 expression. *J Immunol* 2007; **178**: 5871-5878 [PMID: 17442971]
- 92 **Elkington PT**, O'Kane CM, Friedland JS. The paradox of matrix metalloproteinases in infectious disease. *Clin Exp Immunol* 2005; **142**: 12-20 [PMID: 16178851 DOI: 10.1111/j.1365-2249.2005.02840.x]
- 93 **Ferry G**, Lonchamp M, Pennel L, de Nanteuil G, Canet E, Tucker GC. Activation of MMP-9 by neutrophil elastase in an in vivo model of acute lung injury. *FEBS Lett* 1997; **402**: 111-115 [PMID: 9037177]
- 94 **Van den Steen PE**, Proost P, Wuyts A, Van Damme J, Opdenakker G. Neutrophil gelatinase B potentiates interleukin-8 tenfold by aminoterminal processing, whereas it degrades CTAP-III, PF-4, and GRO-alpha and leaves RANTES and MCP-2 intact. *Blood* 2000; **96**: 2673-2681 [PMID: 11023497]
- 95 **Heppner KJ**, Matrisian LM, Jensen RA, Rodgers WH. Expression of most matrix metalloproteinase family members in breast cancer represents a tumor-induced host response. *Am J Pathol* 1996; **149**: 273-282 [PMID: 8686751]
- 96 **Jackson PL**, Xu X, Wilson L, Weathington NM, Clancy JP, Blalock JE, Gaggar A. Human neutrophil elastase-mediated cleavage sites of MMP-9 and TIMP-1: implications to cystic fibrosis proteolytic dysfunction. *Mol Med* 2010; **16**: 159-166 [PMID: 20111696 DOI: 10.2119/molmed.2009.00109]
- 97 **Griese M**, Kappler M, Gaggar A, Hartl D. Inhibition of airway proteases in cystic fibrosis lung disease. *Eur Respir J* 2008; **32**: 783-795 [PMID: 18757703 DOI: 10.1183/09031936.00146807]
- 98 **Greene CM**, McElvaney NG. Proteases and antiproteases in chronic neutrophilic lung disease - relevance to drug discovery. *Br J Pharmacol* 2009; **158**: 1048-1058 [PMID: 19845686 DOI: 10.1111/j.1476-5381.2009.00448.x]
- 99 **Kelly E**, Greene CM, McElvaney NG. Targeting neutrophil elastase in cystic fibrosis. *Expert Opin Ther Targets* 2008; **12**: 145-157 [PMID: 18208364 DOI: 10.1517/14728222.12.2.145]
- 100 **Vega-Carrascal I**, Reeves EP, Niki T, Arikawa T, McNally P, O'Neill SJ, Hirashima M, McElvaney NG. Dysregulation of TIM-3-galectin-9 pathway in the cystic fibrosis airways. *J Immunol* 2011; **186**: 2897-2909 [PMID: 21263071 DOI: 10.4049/jimmunol.1003187]
- 101 **Vandivier RW**, Fadok VA, Hoffmann PR, Bratton DL, Penvari C, Brown KK, Brain JD, Accurso FJ, Henson PM. Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic cell clearance in cystic fibrosis and bronchiectasis. *J Clin Invest* 2002; **109**: 661-670 [PMID: 11877474 DOI: 10.1172/JCI13572]
- 102 **Vega-Carrascal I**, Bergin DA, McElvaney OJ, McCarthy C, Banville N, Pohl K, Hirashima M, Kuchroo VK, Reeves EP, McElvaney NG. Galectin-9 signaling through TIM-3 is involved in neutrophil-mediated Gram-negative bacterial killing: an effect abrogated within the cystic fibrosis lung. *J Immunol* 2014; **192**: 2418-2431 [PMID: 24477913 DOI: 10.4049/jimmunol.1300711]
- 103 **Hartl D**, Latzin P, Hordijk P, Marcos V, Rudolph C, Woischnik M, Krauss-Etschmann S, Koller B, Reinhardt D, Roscher AA, Roos D, Griese M. Cleavage of CXCR1 on neutrophils disables bacterial

- killing in cystic fibrosis lung disease. *Nat Med* 2007; **13**: 1423-1430 [PMID: 18059279 DOI: 10.1038/nm1690]
- 104 **Guyot N**, Butler MW, McNally P, Weldon S, Greene CM, Levine RL, O'Neill SJ, Taggart CC, McElvaney NG. Elafin, an elastase-specific inhibitor, is cleaved by its cognate enzyme neutrophil elastase in sputum from individuals with cystic fibrosis. *J Biol Chem* 2008; **283**: 32377-32385 [PMID: 18799464 DOI: 10.1074/jbc.M803707200]
 - 105 **Taggart CC**, Lowe GJ, Greene CM, Mulgrew AT, O'Neill SJ, Levine RL, McElvaney NG. Cathepsin B, L, and S cleave and inactivate secretory leucoprotease inhibitor. *J Biol Chem* 2001; **276**: 33345-33352 [PMID: 11435427 DOI: 10.1074/jbc.M103220200]
 - 106 **Welsh MJ**, Fick RB. Cystic fibrosis. *J Clin Invest* 1987; **80**: 1523-1526 [PMID: 3316277 DOI: 10.1172/JCI113237]
 - 107 **Hampton MB**, Chambers ST, Vissers MC, Winterbourn CC. Bacterial killing by neutrophils in hypertonic environments. *J Infect Dis* 1994; **169**: 839-846 [PMID: 8133099 DOI: 10.1093/infdis/169.4.839]
 - 108 **Sheppard FR**, Moore EE, McLaughlin N, Kelher M, Johnson JL, Silliman CC. Clinically relevant osmolar stress inhibits priming-induced PMN NADPH oxidase subunit translocation. *J Trauma* 2005; **58**: 752-757; discussion 757 [PMID: 15824651 DOI: 10.1097/01.TA.0000159246.33364.72]
 - 109 **Choi SH**, Lee SW, Hong YS, Jeun JM, Min BW. Selective inhibition of polymorphonuclear neutrophils by resuscitative concentration of hypertonic saline. *Emerg Med J* 2006; **23**: 119-122 [PMID: 16439740 DOI: 10.1136/emj.2004.020651]
 - 110 **Shields CJ**, O'Sullivan AW, Wang JH, Winter DC, Kirwan WO, Redmond HP. Hypertonic saline enhances host response to bacterial challenge by augmenting receptor-independent neutrophil intracellular superoxide formation. *Ann Surg* 2003; **238**: 249-257 [PMID: 12894019 DOI: 10.1097/01.sla.0000080827.77985.fc]
 - 111 **Ciesla DJ**, Moore EE, Musters RJ, Biffi WL, Silliman CA. Hypertonic saline alteration of the PMN cytoskeleton: implications for signal transduction and the cytotoxic response. *J Trauma* 2001; **50**: 206-212 [PMID: 11242283 DOI: 10.1097/00005373-200102000-00004]
 - 112 **Rizoli SB**, Rotstein OD, Parodo J, Phillips MJ, Kapus A. Hypertonic inhibition of exocytosis in neutrophils: central role for osmotic actin skeleton remodeling. *Am J Physiol Cell Physiol* 2000; **279**: C619-C633 [PMID: 10942712]
 - 113 **Bergsson G**, Reeves EP, McNally P, Chotirmall SH, Greene CM, Grealley P, Murphy P, O'Neill SJ, McElvaney NG. LL-37 complexation with glycosaminoglycans in cystic fibrosis lungs inhibits antimicrobial activity, which can be restored by hypertonic saline. *J Immunol* 2009; **183**: 543-551 [PMID: 19542465]
 - 114 **Elkins MR**, Bye PT. Inhaled hypertonic saline as a therapy for cystic fibrosis. *Curr Opin Pulm Med* 2006; **12**: 445-452 [PMID: 17053496 DOI: 10.1097/01.mcp.0000245714.89632.b2]
 - 115 **Wark PA**, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* 2005; **(3)**: CD001506 [PMID: 16034863 DOI: 10.1002/14651858.CD001506.pub2]
 - 116 **Stanley RB**, Becker TS. Injuries of the nasofrontal orifices in frontal sinus fractures. *Laryngoscope* 1987; **97**: 728-731 [PMID: 3586815 DOI: 10.1001/jama.2012.5214]

P- Reviewer: Chen XL, Lin J, Nayci A, Ntoumenopoulos G

S- Editor: Tian YL **L- Editor:** A **E- Editor:** Wu HL



Postoperative fluid management

Selami Ilgaz Kayilioglu, Tolga Dinc, Isa Sozen, Akin Bostanoglu, Mukerrem Cete, Faruk Coskun

Selami Ilgaz Kayilioglu, Tolga Dinc, Isa Sozen, Akin Bostanoglu, Mukerrem Cete, Faruk Coskun, Ankara Numune Training and Research Hospital, Department of General Surgery, 06100 Altindag, Ankara, Turkey

Author contributions: Kayilioglu SI, Dinc T and Coskun F designed the review; Kayilioglu SI, Dinc T, Sozen I, Bostanoglu A and Cete M conducted the literature review; Kayilioglu SI, Dinc T and Coskun F wrote the article; Cete M and Coskun F supervised all the process.

Conflict-of-interest statement: Authors have no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Faruk Coskun, Professor of Surgery, Ankara Numune Training and Research Hospital, Department of General Surgery, Anafartalar Mah. Talatpasa Bul. No. 5, 06100 Altindag, Ankara, Turkey. farukcoskun@mynet.com
Telephone: +90-312-5085075
Fax: +90-312-3103460

Received: November 28, 2014
Peer-review started: November 29, 2014
First decision: January 20, 2015
Revised: February 12, 2015
Accepted: April 1, 2015
Article in press: April 7, 2015
Published online: August 4, 2015

Abstract

Postoperative care units are run by an anesthesiologist or a surgeon, or a team formed of both. Management of postoperative fluid therapy should be done considering both patients' status and intraoperative events. Types

of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. The main goal of fluid resuscitation is to provide adequate tissue perfusion without harming the patient. The endothelial glycocalyx dysfunction and fluid shift to extracellular compartment should be considered wisely. Fluid management must be done based on patient's body fluid status. Patients who are responsive to fluids can benefit from fluid resuscitation, whereas patients who are not fluid responsive are more likely to suffer complications of over-hydration. Therefore, common use of central venous pressure measurement, which is proved to be inefficient to predict fluid responsiveness, should be avoided. Goal directed strategy is the most rational approach to assess the patient and maintain optimum fluid balance. However, accessible and applicable monitoring tools for determining patient's actual fluid need should be further studied and universalized. The debate around colloids and crystalloids should also be considered with goal directed therapies. Advantages and disadvantages of each solution must be evaluated with the patient's specific condition.

Key words: Body fluids; Body fluid compartments; Fluid therapy; Intensive care; Postoperative care

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Types of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. Assessment of the patient's responsiveness to fluid resuscitation should determine the need of extra volume. Due to lack of evidence that supports central venous pressure (CVP) as an indicator of body fluid needs, we should not make our fluid resuscitation decisions based on CVP levels. On the other hand dynamic measures can be used to determine patient's fluid status. Among all fluid management strategies, goal directed strategy is the most rational approach to maintain optimum fluid balance.

Kayilioglu SI, Dinc T, Sozen I, Bostanoglu A, Cete M, Coskun F. Postoperative fluid management. *World J Crit Care Med* 2015; 4(3): 192-201 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/192.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.192>

POSTOPERATIVE FLUID MANAGEMENT

Fluid management is an important part of overall surgical therapy. Proper administration of fluids is critical, especially in patients who undergo major surgeries such as emergency laparotomies, bowel resections and hepatectomy procedures. Body fluid composition may change in minutes or hours, resulting in impaired wound healing and homeostasis. Briefly, choice of strategy in intraoperative and postoperative fluid management may be significant.

We will examine different postoperative fluid management strategies in this review. Postoperative management of patients, who undergo surgery, is carried out by intensive care specialists, anesthesiologists and general surgeons in postoperative care units, in all over the world^[1]. On the other hand, intraoperative management is a quite different expertise, which is totally put into practice by anesthesiologists only, and is not covered in this article. Although postoperative care units are mostly managed by a team of both anesthesiologists and surgeons or only by anesthesiologists in Europe and Japan, surgeons' presence and co-leadership is of great importance in postoperative care. Harmonious with this view, surgeons play the largest role in North America^[1,2].

Types of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. Several debates have been continued about each of these topics. In early times of modern medicine, administering large amounts of fluids was favored, instead of facing the risk of hypovolemia^[3]. In 1961, Shires *et al.*^[4] defined the "third space" fluid deficit as nonfunctional fluid which can be accounted as fluid loss and they suggested use of large quantities of fluids to substitute this functional loss. After this strategy becomes popular, reports of adverse effects of high volume states induced by excessive saline use began to arise. Today, exact amount of fluid to maintain ideal homeostasis is still controversial. Similarly, there are varying types of intravenous fluids and all vary in their biological and chemical properties which results in varying distribution forms and varying effects on homeostasis, vascular integrity, and other hemodynamic variables. Apparently, fluid management is admitted to be an art of medicine and based on personal judgments. Although this approach may not be totally wrong, plenty of evidence acquired by large volume studies should be considered wisely.

Postoperative fluid management plays a key role in providing adequate tissue perfusion, stable

hemodynamics and reducing morbidities related with hemodynamics. Understanding body fluid physiology and possible outcomes of different fluid management strategies is crucial for all surgeons.

BODY FLUID COMPARTMENTS

Total body water is approximately 60% of total body weight. One third of this water is extracellular and it can be divided to as intravascular (20%) and extravascular (80%). The remaining two-third of body water is intracellular, which also exists in intravascular and extravascular compartments. From another perspective, intravascular fluid contains of both intracellular (40%) and extracellular (60%) compounds and plasma is the intravascular-extracellular compound of total body water (approximately 4% of body weight; in example, about 2.8 L in a 70 kg individual).

The endothelium is the separating wall between intravascular and extravascular compartments, thus it is the cell wall that separates the intracellular and extracellular compartments. There are various control mechanisms on these separating walls that regulate volumes of each compartment. Cell membrane is completely permeable to water, whereas it is selectively permeable to ions and organic molecules. It has also the Na⁺/K⁺-adenosine triphosphatase enzyme that actively expels Na⁺ ions and maintains the Na⁺ gradient between compartments. There are also endocrine mechanisms that control the cellular intake of certain molecules, such as glucose.

On the other hand, the earliest theory on vascular barrier by Ernest Starling declared that the hydrostatic pressure gradient in blood vessels creates a flow and the oncotic pressure of interstitial tissue allows only reasonable amount of fluid to cross through endothelium^[5]. Later studies showed the intravascular osmotic pressure is significantly higher than interstitial osmotic pressure, however this doesn't result in interstitial edema^[6]. As a result, this unexplained situation led researchers to look for another actor in this fluid distribution balance. The endothelial glycocalyx is a carbohydrate-rich coating over endothelial surface which is supported by proteoglycans and glycoproteins. It is a dynamic formation, consisting of membrane-bound and soluble molecules^[7]. Existence of this glycocalyx layer forms a distinct space in the interior neighborhood of the endothelium, and there develops a notable oncotic pressure in this particular protein-free space. This definition brings out the "double-layer concept" for the vascular barrier^[6,8,9]. This concept is quite capable of clarifying oncotic pressure balance between two compartments.

WHAT HAPPENS TO THE FLUID BALANCE IN SURGERY?

Homeostasis defines the tendency of the organism to maintain stability and balance. In this manner, body

fluid balance is controlled by previously described compartment mechanisms. On the other hand, any physical intervention may cause imbalance of the body fluids. During relatively long lasting major surgeries, which are performed with general anesthesia, whole intake is controlled by the anesthesiologist and fluid loss happens in numerous different ways such as bleeding, drainage of ascites, urination, insensible water loss and "third space losses". Intraoperative management of acute losses is not covered in this article. However, long term effects of these intraoperative events, such as possible over-hydrating by the anesthesiologist, dehydration, and bleeding should be considered in the postoperative care unit.

The third space is a term for spaces in which body fluids lose their function to affect fluid balance between intravascular and extravascular compartments. In other words, it can be called as non-functional extracellular volume. Bowel lumen, peritoneal and pleural cavities are thought to be the major examples of the third space. Studies that tried to explain the third space loss measured the extracellular volume (ECV) and functional ECV (fECV). fECV is defined as fluid accumulations within the interstitial space combined with plasma. Shires showed that, there is up to 28% loss in extracellular volume after two hours of operative time, during elective surgeries of thirteen adult patients^[4]. Subsequent studies in 1960s support this finding and existence of the third space^[10-12]. However, numerous trials with improved methodology proved that fECV levels do not decrease in or after surgery^[13-16]. This correction of data couldn't be recognized well enough, but still, favored common belief is in the presence and importance of the third space. Current evidence supports that fECV is not negatively affected by surgery, however over-hydration with saline and surgical trauma cause endothelial dysfunction and interstitial edema due to fluid shift to ECV^[13]. In conclusion, "the third space" term should only refer to anatomical cavities like bowel lumen, peritoneum and pleura, and should only be considered in certain cases. Moreover, possible endothelial glycocalyx dysfunction and fluid shift to ECV should be our guiding facts for determining the right strategy in postoperative fluid management.

MONITORING BODY FLUID STATUS

Mostly, the main goal of fluid resuscitation is to provide adequate tissue perfusion without harming the patient. It can be also said that fluid resuscitation is generally the first step in patients with inadequate tissue perfusion. However, it should be kept in mind that infusion of large volumes of fluids to patients who don't have enough preload reserves may result in unbalanced fluid shift to interstitial tissue, having no useful effect on tissue perfusion. Intravenous fluid administration will have no effect on tissue perfusion, unless it increases the stroke volume. Studies show that nearly half of the unstable patients are not hemodynamically

responsive to fluid resuscitation^[17,18]. This means that, fluid resuscitation may not always be the right way to provide adequate tissue perfusion, especially in unstable patients. Thereby, assessment of the patient's responsiveness to fluid resuscitation should determine the need of extra volume.

Thus, we need to determine the actual body fluid status of the patient and build a strategy accordingly. For this purpose, static measures of intravascular volume are being used for decades and central venous pressure (CVP) has been the most favorite tool^[19,20]. CVP is widely believed to indicate general intravascular volume status of the patient. Moreover, many intensivists think that, CVP is directly correlated with right ventricle stroke volume and indirectly correlated with left ventricle stroke volume. However, a systematic review of 24 studies showed no relation between CVP and left ventricle stroke volume^[21]. Due to lack of evidence that supports CVP as an indicator of body fluid needs, we should not make our fluid resuscitation decisions based on CVP levels. Similarly, pulmonary capillary wedge pressure is another static measure of intravascular volume and is incapable of predicting fluid responsiveness, in contrast to the common assumption^[22]. Besides, the two even less favored static measures are left ventricular end-diastolic area and inferior vena caval diameter.

On the other hand, recent studies claim that monitoring of the interactions of heart and lung in mechanically ventilated patients, so called dynamic measures, can be used to determine patient's fluid status. According to Marik *et al.*^[18], non-invasive techniques such as the pulse pressure variation, the stroke volume variation, and systolic pressure variation can significantly predict fluid responsiveness in mechanically ventilated patients. These techniques are based on physiological facts. The patients, whose pulse pressures or stroke volumes are more dependent on intra-thoracic pressure variations provided by the ventilator, tend to be more responsive to fluid resuscitation.

The physiological principles underlying the pulse pressure variation (PPV) and the stroke volume variation (SVV) are based on the effects of increased pleural pressure. As the mechanical ventilator increases the pleural pressure, the increased resistance in the pulmonary system causes a decrease in the right ventricle preload and an increase in the right ventricle afterload. Meanwhile, the left ventricle preload and afterload are affected exactly the opposite way of right ventricle is: Left ventricle preload increases and afterload decreases at the end of inspiration. The pulse pressure and the left ventricle stroke volume are at their highest values at this moment. Afterwards, prolongation of blood transit time through pulmonary system results in a decrease in the left ventricle preload and reduction in the left ventricle stroke volume (and the pulse pressure) during expiratory period^[23,24]. Echocardiographic evaluations of aortic flow velocity and stroke volume and vena caval diameter variation

are two other dynamic parameters based on similar physiological reactions.

Another technique for predicting fluid responsiveness is called the passive leg raising (PLR). While previously mentioned techniques are used for mechanically ventilated patients especially who has no spontaneous breathing, PLR can be used on any patient. Raising the legs to provide a better cardiac preload has been used for a long time in emergency patients. Recently PLR gained interest as a predictor for fluid responsiveness. Monnet pointed out that lifting the legs passively in a lying patient induces a significant blood flow towards the heart^[25]. Therefore, Marik *et al.*^[17] called this physiologic condition as "autotransfusion". In a study on mechanically ventilated patients, PLR-induced changes have been found to be strongly similar with the effects of 300 mL colloid infusion. As a result, PLR simulates the state after fluid administration. In other words, if the patient has enough preload reserve, PLR will increase left ventricle preload and stroke volume correspondingly. It is also been reported that, these effects are reversible, and when legs are returned to their horizontal positions, this preload increasing effect disappears^[25]. Another important point is that PLR reaches its maximal effect in 1 min and its effects disappear gradually in time^[26]. Accordingly, when PLR is used to predict fluid responsiveness changes in arterial pulse pressure^[27], descending aorta blood flow^[28], pulse contour-derived stroke volume, or pulsed Doppler-derived velocity-time integral^[29] should be monitored closely at the first minute^[25].

Briefly, fluid management must be done based on the patient's body fluid status. Patients who are responsive to fluids can benefit from fluid resuscitation, whereas patients who are not fluid responsive are more likely to suffer complications of over-hydration.

Therefore, common use of CVP, which is proved to be inefficient to predict fluid responsiveness, should be avoided and attempts should be made to extend the use of techniques like PLR, pulse pressure variation and the stroke volume variation. Practical tools should be manufactured and made available for common use.

TYPES OF INTRAVENOUS FLUIDS: CRYSTALLOIDS AND COLLOIDS

Intravenous fluids are classified into two main types: Crystalloids and colloids. Each group has its very own characteristics and moreover, each particular solution has its unique properties.

Crystalloids

Crystalloids consist of glucose or sodium chloride (saline) solutions. Osmolarity of the solution determines if the solution is hypotonic, isotonic or hypertonic. Isotonic solutions have the closest osmolarity to plasma and the other solution types are named comparing to plasma osmolarity. Saline solution containing 0.9 g of NaCl in

each liter of water is defined as isotonic saline, and it is the most popular intravenous fluid worldwide. Some widely used saline solutions also contain one or more of these components: potassium, calcium, bicarbonate, lactate, and glucose. Isotonic glucose solution contains 50 g glucose in each liter of water and it is defined as isotonic glucose. Glucose in these solutions is metabolized right after administration and solvent is mixed into total body water. On the other hand, saline solution's high NaCl concentration serves to keep its solvent water in the extracellular compartment. However, any crystalloid solution can freely pass through double barrier of endothelium. This condition causes up to four-fifth of the infused crystalloid to distribute directly into the interstitial compartment^[13,30]. Accordingly, crystalloid infusion in high amounts is related with serious complications, such as pulmonary edema^[31], and hyperchloremic acidosis^[32]. Despite that, colloid solutions are generally imprisoned in intravascular compartment, unless double-barrier of endothelium is impaired. Major advantage of crystalloids to colloids is containing only ions or small sized molecules which can easily be metabolized in reasonable amounts.

Colloids

Colloids can be blood products, such as human albumin solution and fresh frozen plasma, or they can also be synthetic large molecules which are not able to distribute across vascular barrier such as gelatins, dextrans, and hydroxyethyl starches.

Colloids are, like crystalloids, widely used in fluid resuscitation^[33]. Although colloids are thought to be more useful than crystalloids for increasing intravascular volume and providing osmotic pressure, they are both shown to be similarly effective on mortality^[34,35]. Colloid solutions are prepared by dissolving colloid molecules in isotonic saline solutions, or more rarely in other crystalloids.

Endogenous albumin is primarily responsible for intravascular osmotic pressure in healthy subjects. Thus, albumin, as an intravenous colloid solution, makes perfect sense to maintain intravascular colloid pressure. However, like all blood products, it has significant disadvantages, like allergic reactions and (theoretically) infection risks, although it is generally considered safe. Molecular weight of albumin is around 69000 Dalton. Gelatins, dextrans and hydroxyethyl starches (HES) are other common colloid substances. Gelatins are products of biochemical processes executed on bovine collagen. Although there are some concerns about its relation with Creutzfeld-Jacob disease and bovine spongiform encephalitis, there is no solid evidence proving these concerns^[36,37]. Dextrans are polysaccharides that can vary in size. Most common types of dextrans are dextran 70 and dextran 40, which are named after their average molecular weights: 70000 and 40000 Dalton, respectively. Lastly, HES is a nonionic starch derivative, which is synthesized from amylopectin. HESs

also vary in molecular weight, and can be classified as low (70000-130000 Dalton), medium, and high (450000-480000 Dalton) molecular weights. They are also classified by their molar substitution degree, which defines the proportion of glucose molecules that are replaced by hydroxyethyls. HESs are the most commonly used colloids in Europe. Commonly used examples of these colloids are Voluven® (Fresenius Kabi, Bad Homburg, Germany) which is a 130000 Dalton tetra starch, dissolved in saline with substitution degree of 0.4 and HAES-steril® (Fresenius Kabi, Bad Homburg, Germany) which is a 200000 Dalton pentastarch, dissolved in saline with substitution degree of 0.5.

Each type of colloid solution has its unique features. Effect on plasma volume and plasma viscosity, adverse reactions, and side effects on the system are the main concerns while choosing colloid solutions. Every colloid substance has a concentration decrease rate (half-life) in plasma by being metabolized, or by a loss through endothelial barrier and glomerular filtration. Half-life of a colloid determines the amount and the duration of plasma volume expansion. Higher molecular weight colloids tend to stay longer in the intravascular compartment. Besides, some studies point that the dextrans and the HESs provide significantly better expansion of plasma volume than the gelatins^[38-40]. Whereas, some studies indicate that only albumin has significant advantage over other colloids and saline; and none of the other colloids is superior to others regarding plasma volume expansion^[41-43].

All colloids provide a level of expansion in plasma volume and this leads to hemodilution. Hemodilution causes a decrease in plasma viscosity. However, it is known that some colloids cause a total increase in viscosity due to red cell aggregation. High molecular weight dextrans and HESs cause a significant increase in viscosity, while low molecular weight dextrans HESs and albumin solutions decrease both red cell aggregation and plasma viscosity^[44-47]. Colloids have various effects on hemostasis, such as impaired platelet function, decreased factor VIIIC and von Willebrand Factor levels, in addition to previously described hemodilution and altered red cell aggregation^[44,48,49]. Particularly, dextrans are known with their significant antithrombotic effects^[49-51].

Accumulation of colloid substances in the body is possible. Dextrans and gelatins can be metabolized in humans. On the other hand, HESs may also accumulate. Metabolism and filtration of HES is relatively slow and storage in reticulo-endothelial system is not well recognized yet.

All colloids are large molecules and can trigger anaphylaxis of anaphylactoid events. Colloids also have minor anti-inflammatory effects.

Although it has been argued for a long time, there are still no definite rules on "crystalloid vs colloids" issue. There are studies that show crystalloid infusion is related with interstitial edema and worse anastomotic

healing^[31,52,53]. On the other side, it is still arguable that colloid solutions are able to prevent consequences of these negative effects^[54,55]. In a study on pancreaticoduodenectomy patients, who are resuscitated with lactated Ringer's solution (isotonic crystalloid solution; including lactate, potassium and calcium in addition to sodium chloride), the significantly increased interstitial edema in jejunum was shown^[56]. However, colloid use has been reported to have an increasing effect on mortality, in some fairly criticized studies, especially on critically ill patients^[57,58]. On the other hand, CRISTAL trial, which is a multicenter randomized study on critically ill patients, failed to demonstrate this effect on mortality. In contrast, fewer death rates were found within 90 d in colloids group^[54].

Moreover, although colloids are proved to be capable of maintaining efficient plasma volume, they do not appear to have positive effects on renal function. Contrarily, reports had shown significant harmful effects of dextran 40 use on kidney function in the second half of 20th century^[59-61]. Some of the subsequent studies on HESs also revealed negative effects of these solutions on kidneys^[62,63]. Schortgen *et al*^[64] also reported that the use of hyperoncotic colloids and human albumin is significantly associated with renal dysfunction. However, in a multicenter study on over 3000 intensive care patients, no significant relation was detected between HES use and renal dysfunction^[65]. Similarly, in a review of studies with different HES products, no adverse effects on kidneys were reported^[66]. In a randomized clinical multicenter trial, 6997 critically ill patients were randomized into two groups. One group was assigned to receive 4% of albumin and the other group was assigned to receive saline for intravenous resuscitation during 28 d. There was no significant difference between two groups, regarding to mortality, days spent in intensive care unit, days of mechanical ventilation, or days of renal replacement therapy^[67]. In addition to all of these results, it should be taken into consideration that none of the colloid solutions is proved to be directly toxic to the kidneys^[68].

Considering all pros and cons of each solution family, it is still not possible to make a strict evidence based statement about how to use colloids and crystalloids^[57,69]. It should be kept in mind that, crystalloids have less negative effects on hemostasis, immune system and kidneys; whereas colloids may provide a better plasma volume expansion with less interstitial edema in elective surgery patients^[69].

FLUID RESUSCITATION STRATEGIES

Although there has been various different strategies defined in literature in decades, none has been adopted alone by most of the clinicians as the superior strategy. We think that many clinicians tend to keep their accustomed strategy, despite the evidences in the literature. There are studies that compare outcomes

of different strategies of fluid management. Lately, “crystalloids vs colloids” debates are fading, while recent studies mostly focus on the amount of fluid given perioperatively.

Traditional approach to determine the fluid amounts is more likely to generate formulas based on parameters such as patients’ body weights and duration of surgeries. However, there is an evidence that each patient has his/her own body fluid status depending on the type of surgery, comorbid conditions, fluid already administered before, and various other factors. In addition, each patient should be considered as unique and his/her unique status should be monitored closely in the correct ways. As stated before, the main goal of fluid management is to maintain adequate tissue perfusion, with minimized risks of complications of over-hydration, such as pulmonary edema, cerebral edema, and intestinal edema. Both inadequate and excessive fluid administration may increase the stress on the circulatory system, and can affect tissue healing after surgery. From this perspective, without decent monitoring of patient’s current status, any strategy may fail.

Debates about fluid management strategies are gathered around liberal strategy, restricted (conservative) strategy and goal-directed strategy so far. Liberal and restricted strategies are defined by different authors with variable volume ranges. For example, in one study, restricted fluid volume is defined as 1000 mL plus loss through drains^[70], while in another study, patients in restricted fluid volume group were subjected to over 2000 mL fluid on the day of surgery^[71]. These variances make it difficult to consider these studies as a whole. Still, majority of authors studying this subject point out that restrictive strategy has positive effects on gastrointestinal function, wound healing and pulmonary function^[44,70,72-74]. Brandstrup *et al.*^[70] stated that, excessive hydration with crystalloids is related with increased major complications, such as leakage, peritonitis, sepsis, pulmonary edema and bleeding in patients who underwent elective colorectal surgery. Also, intestinal edema is known to be related with increased bacterial translocation and multiple organ dysfunction syndrome rates^[75,76]. It can be concluded that, staying closer to the dehydration level is more reasonable, because it is safer and more efficient than administering large volumes to avoid dehydration. On the other hand, the liberal strategy is superior to the restricted strategy for reducing postoperative nausea, headache, dizziness and vomiting^[77,78].

However, the goal directed strategy (GDS) is totally based on patient’s current data, obtained from monitoring methods (See section: Monitoring body fluid status). Rivers and colleagues, one of the pioneers of this strategy, monitored CVP, mean arterial pressure, serum lactate, and mixed venous oxygen saturation in order to manage therapy in sepsis patients^[79]. Later studies were focused on monitoring hemodynamics,

and the effects of administered fluids on patients. Now, GDS can be defined as an individualized fluid therapy, based on patient’s fluid responsiveness; in other words, “fluid need”. The extra volume, which won’t be able to affect the left ventricle stroke volume is regarded as unnecessary; and as a matter of fact, hazardous. It makes perfect sense to totally evaluate patient’s needs and replace what is needed. Still, efficiency of GDS is limited with the power of our monitoring tools, which is determined by accessibility, applicability of the tools and the quality of information we acquire from them.

PPV and SVV are defined to monitor the fluid need of the patient dynamically as it is stated above^[18]. Esophageal Doppler monitoring of cardiac volumes and aortic flow are also one of the helpful tools in GDS. In a systematic review of esophageal Doppler guided GDS studies; reduced hospital stay, fewer ICU admissions, and less inotropes usage were detected in GDS group^[80]. In a single center, blinded, prospective controlled trial, 128 patients who underwent colorectal resection were randomized into two groups. Each group was managed with esophageal Doppler or CVP guided fluid therapy during surgery. Intraoperative Doppler guided fluid management was associated with decrease in the duration of hospital stay^[81]. A randomized controlled study on 108 elective colorectal surgery patients also showed shorter hospital stay and decreased morbidity in GDS group^[82]. GDS is also advantageous in patients who undergo major surgery^[79]. A systematic review and meta-analysis studies by Hamilton on major surgery patients state that preemptive hemodynamic monitoring reduces mortality and morbidity^[83]. Similarly, Poeze *et al.*^[84] showed that efforts to achieve an optimized hemodynamic condition resulted in a decreased mortality rate, in their meta-analysis study in 2005. Another meta-analysis also shows that GDS reduces both major and minor gastrointestinal complications after surgery^[85].

In contrast with these studies, in a multicenter study, which included 762 high risk patients in 56 intensive care units, no significant effects of GDS were found. In this study, patients were randomly assigned to cardiac-index group, mixed venous oxygen-saturation group and standard therapy group. Predetermined hemodynamic targets were reached significantly better in the control group. There were no significant differences among the three groups, regarding mortality at six months. Even the subgroup analysis of patients, whose predetermined hemodynamic targets have been reached successfully, showed similar mortality rates among the three groups. Moreover, the number of dysfunctional organs and the duration of stay in the intensive care unit were similar in all groups^[86].

Despite these evidences, low accessibility and applicability of esophageal Doppler are the major disadvantages of this method. This leads researchers to search for a more accessible and applicable method for common use in postoperative care unit, such as non-

invasive pulse oximetry and invasive arterial pressure measurement. Thus, predictive value of pulse pressure variation, systolic pressure variation and stroke volume variation tests for fluid responsiveness are defined^[17]. All of these tests are applicable in an average postoperative care unit. However, the true value of these tests should be evaluated by larger studies. After that, optimization of patient monitoring devices should be done accordingly. Moreover, even PLR alone can provide important information about fluid responsiveness and lead the intensivists for GDS.

Since there is still insufficient number of randomized controlled trials with standardized criteria, the fluid management debates are going on. A consensus on criteria for each fluid management strategy should be made. We think that the related studies from all around the world with defined criteria are going to reveal the true value of each strategy.

Each surgeon should keep in mind that the patient is totally managed by the anesthesiologist during the surgery, so depending on the anesthesiologist's preference on fluid strategy, patient's fluid status after surgery may vary widely. Besides, intraoperative bleeding and other causes of surgical fluid loss should also be considered. During or after the surgery, the blood loss in patients with low hemoglobin levels is generally managed with erythrocyte suspensions. However, in patients with reasonable hemoglobin levels, appropriate fluid strategy should be chosen to avoid complications of transfusion. We think that determining the actual fluid status and the needs of a postoperative patient, by using monitoring tools and examining the report of the anesthesiologist, is of great importance.

CONCLUSION

Postoperative care units can be managed by an anesthesiologist, a surgeon or a team composed of both. Management of postoperative fluid therapy should be done considering both patients' unique status and intraoperative events. Thus, surgeons must be aware of pros and cons of current fluid management strategies and their effects on surgical outcome. Although there has been a significant progress on fluid status monitoring and fluid management strategies, most clinicians still prefer their traditional approaches for postoperative fluid management. This tendency towards empirical fluid management can be replaced by evidence based strategies, only if significant benefits of new strategies are proved with multicenter randomized controlled trials which use standardized criteria. GDS is the most rational approach to assess the patient and maintain optimum fluid balance. However, accessible and applicable monitoring tools for determining patient's actual fluid need should be further studied and universalized. The debate around colloids and crystalloids should also be considered with goal directed therapies. Advantages and disadvantages of each solution must be evaluated with

the patient's specific condition.

REFERENCES

- 1 Linke GR, Mieth M, Hofer S, Trierweiler-Hauke B, Weitz J, Martin E, Büchler MW. Surgical intensive care unit - essential for good outcome in major abdominal surgery? *Langenbecks Arch Surg* 2011; **396**: 417-428 [PMID: 21369847 DOI: 10.1007/s00423-011-0758-y]
- 2 Johnson JL, Moore EE, Aasen AO, Roky MA, Wang JE, Alsanea O, Aikawa N, Neira JA, Tisminetzky GJ. The role of the surgeon as intensivist: an international perspective. *Curr Opin Crit Care* 2006; **12**: 357-369 [PMID: 16810049 DOI: 10.1097/01.ccx.0000235215.71612.a9]
- 3 Bamboat ZM, Bordeianou L. Perioperative fluid management. *Clin Colon Rectal Surg* 2009; **22**: 28-33 [PMID: 20119553 DOI: 10.1055/s-0029-1202883]
- 4 Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; **154**: 803-810 [PMID: 13912109]
- 5 Starling EH. On the Absorption of Fluids from the Connective Tissue Spaces. *J Physiol* 1896; **19**: 312-326 [PMID: 16992325]
- 6 Adamson RH, Lenz JF, Zhang X, Adamson GN, Weinbaum S, Curry FE. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. *J Physiol* 2004; **557**: 889-907 [PMID: 15073281 DOI: 10.1113/jphysiol.2003.058255]
- 7 Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch* 2007; **454**: 345-359 [PMID: 17256154 DOI: 10.1007/s00424-007-0212-8]
- 8 Strunden MS, Heckel K, Goetz AE, Reuter DA. Perioperative fluid and volume management: physiological basis, tools and strategies. *Ann Intensive Care* 2011; **1**: 2 [PMID: 21906324 DOI: 10.1186/2110-5820-1-2]
- 9 Rehm M, Zahler S, Lötsch M, Welsch U, Conzen P, Jacob M, Becker BF. Endothelial glycocalyx as an additional barrier determining extravasation of 6% hydroxyethyl starch or 5% albumin solutions in the coronary vascular bed. *Anesthesiology* 2004; **100**: 1211-1223 [PMID: 15114220]
- 10 Carrico CJ, Coln CD, Lightfoot SA, Allsman A, Shires GT. Extracellular fluid volume replacement in hemorrhagic shock. *Surg Forum* 1963; **14**: 10-12 [PMID: 14064470]
- 11 Shires T, Coln D, Carrico J, Lightfoot S. Fluid therapy in hemorrhagic shock. *Arch Surg* 1964; **88**: 688-693 [PMID: 14107023]
- 12 Fukuda Y, Fujita T, Shibuya J, Albert SN. The distribution between the intravascular and interstitial compartments of commonly utilized replacement fluids. *Anesth Analg* 1977; **48**: 831-838 [PMID: 4897746]
- 13 Jacob M, Chappell D, Rehm M. The 'third space'--fact or fiction? *Best Pract Res Clin Anaesthesiol* 2009; **23**: 145-157 [PMID: 19653435]
- 14 Gumpert JR, Zollinger RM, Riddell AG. Proceedings: the measurement of extracellular fluid volume with radiobromide simultaneous plasma and lymph disappearance in man. *Br J Surg* 1973; **60**: 903 [PMID: 4584778]
- 15 Breckenridge IM, Digerness SB, Kirklin JW. Validity of concept of increased extracellular fluid after open heart surgery. *Surg Forum* 1969; **20**: 169-171 [PMID: 4910576]
- 16 Nielsen OM, Engell HC. Extracellular fluid volume and distribution in relation to changes in plasma colloid osmotic pressure after major surgery. A randomized study. *Acta Chir Scand* 1985; **151**: 221-225 [PMID: 3892993]
- 17 Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2011; **1**: 1 [PMID: 21906322 DOI: 10.1186/2110-5820-1-1]
- 18 Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness

- in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642-2647 [PMID: 19602972 DOI: 10.1097/CCM.0b013e3181a590da]
- 19 **McIntyre LA**, Hébert PC, Fergusson D, Cook DJ, Aziz A; Canadian Critical Care Trials Group. A survey of Canadian intensivists' resuscitation practices in early septic shock. *Crit Care* 2007; **11**: R74 [PMID: 17623059 DOI: 10.1186/cc5962]
 - 20 **Kastrup M**, Markewitz A, Spies C, Carl M, Erb J, Grosse J, Schirmer U. Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. *Acta Anaesthesiol Scand* 2007; **51**: 347-358 [PMID: 17096667 DOI: 10.1111/j.1399-6576.2006.01190.x]
 - 21 **Marik PE**, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 2013; **41**: 1774-1781 [PMID: 23774337 DOI: 10.1097/CCM.0b013e31828a25fd]
 - 22 **Solus-Biguenet H**, Fleyfel M, Tavernier B, Kipnis E, Onimus J, Robin E, Lebuffe G, Decoene C, Pruvot FR, Vallet B. Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth* 2006; **97**: 808-816 [PMID: 16980709 DOI: 10.1093/bja/ael250]
 - 23 **Michard F**, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000; **4**: 282-289 [PMID: 11094507 DOI: 10.1186/cc710]
 - 24 **Theres H**, Binkau J, Laule M, Heinze R, Hundertmark J, Blobner M, Erhardt W, Baumann G, Stangl K. Phase-related changes in right ventricular cardiac output under volume-controlled mechanical ventilation with positive end-expiratory pressure. *Crit Care Med* 1999; **27**: 953-958 [PMID: 10362419]
 - 25 **Monnet X**, Teboul JL. Passive leg raising. *Intensive Care Med* 2008; **34**: 659-663 [PMID: 18214429 DOI: 10.1007/s00134-008-0994-y]
 - 26 **Monnet X**, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; **34**: 1402-1407 [PMID: 16540963 DOI: 10.1097/01.CCM.0000215453.11735.06]
 - 27 **Boulain T**, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. *Chest* 2002; **121**: 1245-1252 [PMID: 11948060]
 - 28 **Lafanechère A**, Pène F, Goulenok C, Delahaye A, Mallet V, Choukroun G, Chiche JD, Mira JP, Cariou A. Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care* 2006; **10**: R132 [PMID: 16970817 DOI: 10.1186/cc5044]
 - 29 **Lamia B**, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007; **33**: 1125-1132 [PMID: 17508199 DOI: 10.1007/s00134-007-0646-7]
 - 30 **Kinsella SM**, Pirlet M, Mills MS, Tuckey JP, Thomas TA. Randomized study of intravenous fluid preload before epidural analgesia during labour. *Br J Anaesth* 2000; **85**: 311-313 [PMID: 10992845]
 - 31 **Stein L**, Beraud JJ, Morissette M, Luz PD, Weil MH, Shubin H. Pulmonary edema during volume infusion. *Circulation* 1975; **52**: 483-489 [PMID: 1157248]
 - 32 **Waters JH**, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 2001; **93**: 817-822 [PMID: 11574339]
 - 33 **Yim JM**, Vermeulen LC, Erstad BL, Matuszewski KA, Burnett DA, Vlasses PH. Albumin and nonprotein colloid solution use in US academic health centers. *Arch Intern Med* 1995; **155**: 2450-2455 [PMID: 7503604]
 - 34 **Alderson P**, Bunn F, Lefebvre C, Li WP, Li L, Roberts I, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev* 2004; **(4)**: CD001208 [PMID: 15495011 DOI: 10.1002/14651858.CD001208.pub2]
 - 35 **Roberts I**, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2004; **(4)**: CD000567 [PMID: 15495001 DOI: 10.1002/14651858.CD000567.pub2]
 - 36 **Taylor DM**. Inactivation of TSE agents: safety of blood and blood-derived products. *Transfus Clin Biol* 2003; **10**: 23-25 [PMID: 12668184]
 - 37 **Grobbs AH**, Steele PJ, Somerville RA, Taylor DM, Schreuder BE. Inactivation of the BSE agent by the heat and pressure process for manufacturing gelatine. *Vet Rec* 2005; **157**: 277-281 [PMID: 16157568]
 - 38 **Lamke LO**, Liljedahl SO. Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 1976; **5**: 93-102 [PMID: 69313]
 - 39 **Mortelmans YJ**, Vermaut G, Verbruggen AM, Arnout JM, Vermeylen J, Van Aken H, Mortelmans LA. Effects of 6% hydroxyethyl starch and 3% modified fluid gelatin on intravascular volume and coagulation during intraoperative hemodilution. *Anesth Analg* 1995; **81**: 1235-1242 [PMID: 7486110]
 - 40 **Van der Linden PJ**, De Hert SG, Deraedt D, Cromheecke S, De Decker K, De Paep R, Rodrigus I, Daper A, Trenchant A. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. *Anesth Analg* 2005; **101**: 629-634, table of contents [PMID: 16115963 DOI: 10.1213/01.ANE.0000175216.53374.27]
 - 41 **Dubniks M**, Persson J, Grände PO. Plasma volume expansion of 5% albumin, 4% gelatin, 6% HES 130/0.4, and normal saline under increased microvascular permeability in the rat. *Intensive Care Med* 2007; **33**: 293-299 [PMID: 17119921 DOI: 10.1007/s00134-006-0454-5]
 - 42 **Persson J**, Grände PO. Volume expansion of albumin, gelatin, hydroxyethyl starch, saline and erythrocytes after haemorrhage in the rat. *Intensive Care Med* 2005; **31**: 296-301 [PMID: 15609019 DOI: 10.1007/s00134-004-2510-3]
 - 43 **Beyer R**, Harmening U, Rittmeyer O, Zielmann S, Mielck F, Kazmaier S, Kettler D. Use of modified fluid gelatin and hydroxyethyl starch for colloidal volume replacement in major orthopaedic surgery. *Br J Anaesth* 1997; **78**: 44-50 [PMID: 9059203]
 - 44 **Grocott MP**, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesth Analg* 2005; **100**: 1093-1106 [PMID: 15781528 DOI: 10.1213/01.ANE.0000148691.33690.AC]
 - 45 **Freyburger G**, Dubreuil M, Boisseau MR, Janvier G. Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution. *Br J Anaesth* 1996; **76**: 519-525 [PMID: 8652324]
 - 46 **Korosue K**, Heros RC, Ogilvy CS, Hyodo A, Tu YK, Graichen R. Comparison of crystalloids and colloids for hemodilution in a model of focal cerebral ischemia. *J Neurosurg* 1990; **73**: 576-584 [PMID: 1697903 DOI: 10.3171/jns.1990.73.4.0576]
 - 47 **Neff TA**, Fischler L, Mark M, Stocker R, Reinhart WH. The influence of two different hydroxyethyl starch solutions (6% HES 130/0.4 and 200/0.5) on blood viscosity. *Anesth Analg* 2005; **100**: 1773-1780 [PMID: 15920212 DOI: 10.1213/01.ANE.0000149326.45137.9A]
 - 48 **de Jonge E**, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29**: 1261-1267 [PMID: 11395618]
 - 49 **Aberg M**, Hedner U, Bergentz SE. Effect of dextran on factor VIII (antihemophilic factor) and platelet function. *Ann Surg* 1979; **189**: 243-247 [PMID: 426556]
 - 50 **Jones CI**, Payne DA, Hayes PD, Naylor AR, Bell PR, Thompson MM, Goodall AH. The antithrombotic effect of dextran-40 in man is due to enhanced fibrinolysis in vivo. *J Vasc Surg* 2008; **48**: 715-722 [PMID: 18572351 DOI: 10.1016/j.jvs.2008.04.008]
 - 51 **Salemark L**, Wieslander JB, Dougan P, Arnljots B. Studies of the antithrombotic effects of dextran 40 following microarterial trauma. *Br J Plast Surg* 1991; **44**: 15-22 [PMID: 1704269]

- 52 **Baum TD**, Wang H, Rothschild HR, Gang DL, Fink MP. Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. *Circ Shock* 1990; **30**: 385-397 [PMID: 1693551]
- 53 **Marjanovic G**, Villain C, Timme S, zur Hausen A, Hoepfner J, Makowiec F, Holzner P, Hopt UT, Obermaier R. Colloid vs. crystalloid infusions in gastrointestinal surgery and their different impact on the healing of intestinal anastomoses. *Int J Colorectal Dis* 2010; **25**: 491-498 [PMID: 19943164 DOI: 10.1007/s00384-009-0854-4]
- 54 **Annane D**, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, Preiser JC, Outin H, Troché G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Abroug F, Berger P, Clec'h C, Cousson J, Thibault L, Chevret S. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA* 2013; **310**: 1809-1817 [PMID: 24108515 DOI: 10.1001/jama.2013.280502]
- 55 **Perel P**, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2007; **(4)**: CD000567 [PMID: 17943746 DOI: 10.1002/14651858.CD000567.pub3]
- 56 **Prien T**, Backhaus N, Pelster F, Pircher W, Bunte H, Lawin P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *J Clin Anesth* 1990; **2**: 317-323 [PMID: 1702977]
- 57 **Choi PT**, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; **27**: 200-210 [PMID: 9934917]
- 58 **Schierhout G**, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998; **316**: 961-964 [PMID: 9550953]
- 59 **Mailloux L**, Swartz CD, Capizzi R, Kim KE, Onesti G, Ramirez O, Brest AN. Acute renal failure after administration of low-molecular weight dextran. *N Engl J Med* 1967; **277**: 1113-1118 [PMID: 6054998 DOI: 10.1056/NEJM196711232772103]
- 60 **Diomi P**, Ericsson JL, Matheson NA, Shearer JR. Studies on renal tubular morphology and toxicity after large doses of dextran 40 in the rabbit. *Lab Invest* 1970; **22**: 355-360 [PMID: 5429535]
- 61 **Biesenbach G**, Kaiser W, Zazgornik J. Incidence of acute oligoanuric renal failure in dextran 40 treated patients with acute ischemic stroke stage III or IV. *Ren Fail* 1997; **19**: 69-75 [PMID: 9044453]
- 62 **Legendre C**, Thervet E, Page B, Percheron A, Noël LH, Kreis H. Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342**: 248-249 [PMID: 7686994]
- 63 **Brunkhorst FM**, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehnthopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-139 [PMID: 18184958 DOI: 10.1056/NEJMoa070716]
- 64 **Schortgen F**, Girou E, Deye N, Brochard L. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med* 2008; **34**: 2157-2168 [PMID: 18685828 DOI: 10.1007/s00134-008-1225-2]
- 65 **Sakr Y**, Payen D, Reinhart K, Sipmann FS, Zavala E, Bewley J, Marx G, Vincent JL. Effects of hydroxyethyl starch administration on renal function in critically ill patients. *Br J Anaesth* 2007; **98**: 216-224 [PMID: 17251213 DOI: 10.1093/bja/aei333]
- 66 **Boldt J**, Priebe HJ. Intravascular volume replacement therapy with synthetic colloids: is there an influence on renal function? *Anesth Analg* 2003; **96**: 376-382, table of contents [PMID: 12538180]
- 67 **Finfer S**, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350**: 2247-2256 [PMID: 15163774 DOI: 10.1056/NEJMoa040232]
- 68 **Roche AM**, James MF. Colloids and crystalloids: does it matter to the kidney? *Curr Opin Crit Care* 2009; **15**: 520-524 [PMID: 19829107 DOI: 10.1097/MCC.0b013e328332f686]
- 69 **Velanovich V**. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. *Surgery* 1989; **105**: 65-71 [PMID: 2911805]
- 70 **Brandstrup B**, Tønnesen H, Beier-Holgersen R, Hjortso E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lannig C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilmann D, Christensen AM, Graungaard B, Pott F. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; **238**: 641-648 [PMID: 14578723 DOI: 10.1097/01.sla.0000094387.50865.23]
- 71 **MacKay G**, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* 2006; **93**: 1469-1474 [PMID: 17078116 DOI: 10.1002/bjs.5593]
- 72 **Lobo SM**, Ronchi LS, Oliveira NE, Brandão PG, Froes A, Cunrath GS, Nishiyama KG, Netinho JG, Lobo FR. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care* 2011; **15**: R226 [PMID: 21943111 DOI: 10.1186/cc10466]
- 73 **Nisanevich V**, Felsenstein I, Almog G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; **103**: 25-32 [PMID: 15983453]
- 74 **Rahbari NN**, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg* 2009; **96**: 331-341 [PMID: 19283742 DOI: 10.1002/bjs.6552]
- 75 **Baker JW**, Deitch EA, Li M, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *J Trauma* 1988; **28**: 896-906 [PMID: 3294427]
- 76 **Wilmore DW**, Smith RJ, O'Dwyer ST, Jacobs DO, Ziegler TR, Wang XD. The gut: a central organ after surgical stress. *Surgery* 1988; **104**: 917-923 [PMID: 3055397]
- 77 **Maharaj CH**, Kallam SR, Malik A, Hassett P, Grady D, Laffey JG. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. *Anesth Analg* 2005; **100**: 675-682, table of contents [PMID: 15728051 DOI: 10.1213/01.ANE.0000148684.64286.36]
- 78 **Moretti EW**, Robertson KM, El-Moalem H, Gan TJ. Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. *Anesth Analg* 2003; **96**: 611-617, table of contents [PMID: 12538221]
- 79 **Rivers EP**, Nguyen HB, Huang DT, Donnino M. Early goal-directed therapy. *Crit Care Med* 2004; **32**: 314-315; author reply 315 [PMID: 14707615 DOI: 10.1097/01.CCM.0000104937.09370.53]
- 80 **Abbas SM**, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia* 2008; **63**: 44-51 [PMID: 18086070 DOI: 10.1111/j.1365-2044.2007.05233.x]
- 81 **Wakeling HG**, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR, Fleming SC. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95**: 634-642 [PMID: 16155038 DOI: 10.1093/bja/aei223]
- 82 **Noblett SE**, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; **93**: 1069-1076 [PMID: 16888706 DOI: 10.1002/bjs.5454]
- 83 **Hamilton MA**. Perioperative fluid management: progress despite lingering controversies. *Cleve Clin J Med* 2009; **76** Suppl 4: S28-S31 [PMID: 19880832 DOI: 10.3949/ccjm.76.s4.05]
- 84 **Poeze M**, Greve JW, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. *Crit Care* 2005; **9**: R771-R779 [PMID: 16356226 DOI: 10.1186/cc3902]
- 85 **Giglio MT**, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major

surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **103**: 637-646 [PMID: 19837807 DOI: 10.1093/bja/aep279]

86 **Gattinoni L**, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti

A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO₂ Collaborative Group. *N Engl J Med* 1995; **333**: 1025-1032 [PMID: 7675044 DOI: 10.1056/NEJM199510193331601]

P- Reviewer: Gurjar M, Wheeler DS **S- Editor:** Ma YJ **L- Editor:** A
E- Editor: Wu HL



Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums

Sachin Gupta, Ravindranath Tiruvoipati, Cameron Green, John Botha, Huy Tran

Sachin Gupta, Ravindranath Tiruvoipati, Cameron Green, John Botha, Department of Intensive Care Medicine, Frankston Hospital, Frankston VIC 3199, Australia

Sachin Gupta, Ravindranath Tiruvoipati, John Botha, School of Public Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Victoria 3800, Australia

Huy Tran, Department of Oncology, Frankston Hospital, Frankston VIC 3199, Australia

Author contributions: Gupta S contributed to conception and design, drafting the manuscript and revising it critically for important intellectual content; Tiruvoipati R, Green C and Botha J contributed to drafting the manuscript and revising it critically for important intellectual content; Tran H contributed to conception and design, drafting the manuscript and revising it critically for important intellectual content, overall supervision; all authors had given final approval of the version to be published.

Conflict-of-interest statement: None of the authors have any conflicts of interests (including but not limited to commercial, personal, political, intellectual, or religious interests) in relation to this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Ravindranath Tiruvoipati, Associate Professor, Department of Intensive Care Medicine, Frankston Hospital, 2 Hastings Rd, Frankston VIC 3199, Australia. travindranath@hotmail.com
Telephone: +61-4-31279347
Fax: +61-3-97847398

Received: October 3, 2014
Peer-review started: October 3, 2014
First decision: December 26, 2014

Revised: February 25, 2015

Accepted: May 11, 2015

Article in press: May 14, 2015

Published online: August 4, 2015

Abstract

Thrombocytopenia is often noted in critically ill patients. While there are many reasons for thrombocytopenia, the use of heparin and its derivatives is increasingly noted to be associated with thrombocytopenia. Heparin induced thrombocytopenia syndrome (HITS) is a distinct entity that is characterised by the occurrence of thrombocytopenia in conjunction with thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin. HITS is an immunologic disorder mediated by antibodies to heparin-platelet factor 4 (PF4) complex. HITS is an uncommon cause of thrombocytopenia. Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%. It is a complex problem which may cause diagnostic dilemmas and management conundrum. The diagnosis of HITS centers around detection of antibodies against PF4-heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Several anticoagulants are used in management of HITS. In this review we discuss the incidence, pathogenesis, diagnosis and management of HITS.

Key words: Heparin; Thrombocytopenia; Critically ill; Diagnosis; Management

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Thrombocytopenia is common in critically ill patients. While there are several causes of thrombocytopenia, heparin induced thrombocytopenia syndrome (HITS) is an uncommon cause often difficult to diagnose and manage. This article summarises the current diagnostic techniques and management options with a focus on critically ill patients with HITS.

Gupta S, Tiruvoipati R, Green C, Botha J, Tran H. Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums. *World J Crit Care Med* 2015; 4(3): 202-212 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/202.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.202>

INTRODUCTION

It has been over 90 years since the discovery of heparin^[1], and by the 1930s heparin was being used clinically as an anticoagulant^[2]. Embolic events during heparin therapy were first described in 1957 and were followed by subsequent reports; however thrombocytopenia as a result of heparin therapy was not described until 1969^[3-6]. The central features of heparin induced thrombocytopenia (HIT) syndrome (HITS) - thrombocytopenia, thrombosis and its immune pathogenesis - weren't recognized until the early 1970s^[7].

Heparin and its derivatives are used frequently in the critically ill, either as thromboprophylaxis or for anticoagulation in patients with thromboembolic diseases. Thrombocytopenia occurs in 15%-58% of ICU patients^[8,9]. Critically ill patients might suffer from a variety of acquired thrombotic risk factors related both to a host of chronic conditions such as obesity, hypertension, and diabetes mellitus, as well as acutely acquired conditions such as the postoperative state, sepsis, trauma, malignancy, other clonal disorders, etc.^[10]. Hence, diagnosis of HIT syndrome is one of exclusion in the critically ill.

As HIT syndrome is a highly prothrombotic state, affected patients require ongoing anticoagulation with alternative anticoagulation such as the use of antithrombin anticoagulants or anti factor Xa agents^[11,12].

As none of these agents have effective antidotes, management of bleeding associated with these agents is fraught with uncertainty.

HITS has been classified into two subtypes: HITS type 1: Benign non-immune condition occurring in 30%-40% patients exposed to heparin. platelets counts rarely fall below 100000/mcl. Heparin can be safely continued in this scenario and this condition is not discussed any further in the review; HITS type 2: Life threatening condition caused by antibodies against complexes of platelet factor 4 (PF4) and heparin, though occasionally other antigens may be implicated. Further discussion will relate to "type 2 HITS" only.

In this review, we focus on diagnostic dilemmas and management challenges associated with this complex problem.

PATHOGENESIS

Heparin mediated thrombocytopenia is an immunologic disorder mediated by antibodies to heparin-PF4 complex^[13-16]. The Fab fragments from the IgG subclass of antibodies to PF4 bind platelet associated PF4. The Fc fragments of these antibodies bind to FcγIIa receptors on the same or adjacent platelets, resulting in cross linking causing platelet activation. This results in generation of platelet microparticles that have procoagulant activity. This prothrombotic phenomenon is the principal difference between thrombocytopenia induced by heparin and other drugs such as quinine^[17]. This marked release of the platelet microparticles is associated with massive thrombin generation, which explains the increased risk of thrombosis associated with HITS^[18]. Significantly fewer platelet microparticles are generated in the presence of very high amounts of Heparin or in its absence, suggesting a stoichiometric relationship between HIT-IgG antibodies and heparin^[17]. In addition to the increased thrombin generation in HITS, HITS antibodies also bind to endothelium-bound heparin resulting in release of tissue factor (TF) contributing to the overall prothrombotic state^[19]. Recently, Monocytes have been found to bind hPF4 onto their surface and form antigenic complexes leading to monocyte activation and ultimately culminating in expression of TF. Both monocyte and endothelial activation may explain recurrence of thrombosis in many patients treated with direct thrombin inhibitors as none of them target these cells^[20]. This may also explain the fact that HITS predisposes to both arterial and venous thrombosis even though it is primarily a platelet activation disorder. HIT-IgG antibodies also inhibit the generation of activated protein C by thrombin/thrombomodulin in the presence of PF4, augmenting the thrombotic state^[21].

It seems that there might be a crucial period of exposure to heparin in patients who develop HITS. Patients, who suffer from conditions associated with high amounts of PF4 release prior to exposure to heparin, tend to be at a higher risk of developing HITS. For example, amongst elective hip replacement patients who receive preoperative low-molecular weight heparin (LMWH) are at a lower risk of HITS as compared to patients who receive post-operative thromboprophylaxis. This phenomenon of "point immunization" is probably explained by the fact that stoichiometrically optimal concentrations of heparin-PF4 are most likely to occur when PF4 is released prior to exposure to heparin^[22]. Free nucleic acids in plasma can induce similar conformational changes in PF-4 as are induced by heparin, mainly because of the highly anionic Phosphate entities on the nucleic acid molecules. This finding may further explain the propensity for certain subgroups of patients (such as those with major

tissue damage) to develop pathological antibodies to heparin-PF4 complexes^[23].

Two key determinants of antigenicity of a heparin preparation are chain length (approximately 1000 Da) and minimal amount of sulfation per saccharide unit. This explains lower risk of HITS with LMWH preparations as compared to unfractionated heparin (UFH)^[24].

Occasionally, HITS can be caused by antibodies to other antigens such as neutrophil activating peptide-2 or interleukin 8.

EPIDEMIOLOGY

Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%^[25]. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%^[26]. The incidence of HITS varies widely depending on the preparation of heparin, sex of the patients, and clinical population. The risk of HITS is higher amongst women [Odds ratio (OR) = 2.37]; among surgical patients as compared with medical patients (OR = 3.25); and patients on UFH vs patients receiving LMWH (OR = 5.29)^[27]. Amongst surgical patients, although post-cardiac surgery patients tend to have a higher risk of developing HIT-IgG than post-orthopaedic surgical group (20% vs 3.2%), patients are much more likely to develop HITS after Orthopaedic surgery (OR = 21.1)^[28]. Patients with major trauma are more likely to be Heparin-PF4 antibody positive and develop HITS as compared to patients with minor trauma^[29]. HITS is very rare in obstetric or pediatric patients.

CLINICAL FEATURES

Heparin induced thrombocytopenia is characterized by thrombocytopenia and thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin.

Thrombocytopenia

Onset of thrombocytopenia is usually between 5-10 d after the exposure, but it is faster (within a few hours to a day) if the patient has been exposed to heparin within 100 d of current exposure^[30].

Platelet count usually drops to 50% or less of the baseline platelet count. Drop in platelet counts 30%-50% of baseline occurs in 10% of the cases^[25].

Platelet counts usually do not fall below 20000/mcl. Lower platelet counts may be observed if HITS causes disseminated intravascular coagulation (DIC).

Bleeding is very rare as a complication of thrombocytopenia.

Recovery typically takes 4-14 d after cessation of heparin.

Pattern of thrombocytopenia occurring after the inciting event (such as cardiothoracic surgery) is important as well. A continuous decline after cardiopulmonary bypass is less likely to be due to HITS. A fall

in platelet count of at least 40% between 5-10 d post cardiopulmonary bypass is likely to be due to HITS^[31].

Thrombotic manifestations

Thrombotic manifestations develop in 20%-50% of the patients. HITS that is not associated with thrombotic phenomena is known as "isolated HITS".

Thrombosis can affect both arterial and venous beds. However, Venous thromboembolic complications are twice as likely as compared to arterial thrombotic phenomena. About 10%-20% patients suffer DIC.

Risk of thrombosis is higher for days to weeks after heparin is discontinued, even after normalization of the platelet counts^[11].

Risk of thrombosis is higher in patients with higher level of antibodies to PF4-heparin complexes^[32].

Other clinical manifestations that should raise the suspicion of HITS in appropriate clinical scenario: (1) acute anaphylactoid/anaphylactic reactions after heparin administration: Heparin induced anaphylactoid and anaphylactic reactions are two distinct pathophysiological entities. Heparin induced anaphylactoid reactions are due to activation of platelets and leukocytes in patients harbouring anti heparin-PF4 antibodies, typically administered a heparin bolus after prior exposure to heparin. Heparin induced anaphylactic reaction is due to a contaminant (oversulphated chondroitin sulphate or OSCS) activating the contact system resulting in the clinical manifestations. However, patients exposed to OSCS contaminated heparin are more likely to develop pathological HITS antibodies^[33]; (2) heparin induced skin lesions: These painful or pruritic necrotic lesions develop at the site of injection, beginning on day 5 or later after exposure to heparin or LMWH. Non-necrotic lesions at the injection sites are almost always due to delayed hypersensitivity to heparin rather than a manifestation of HITS, especially after exposure to LMWH rather than Unfractionated heparin^[34]; (3) heparin induced skin necrosis and venous gangrene: especially in the presence of coumarin, attributed to both macro and micro vascular thrombosis with preserved arterial flow. Inhibition of activated protein C by heparin PF4 antibodies could be a strong contributory factor^[21]; and (4) transient global amnesia^[35].

These manifestations curiously, tend to occur in the absence of thrombocytopenia^[25].

DIAGNOSIS

The diagnosis of HITS centers around detection of antibodies against PF4-Heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Before elaborating further on the diagnostic assays, it is vital to consider the following

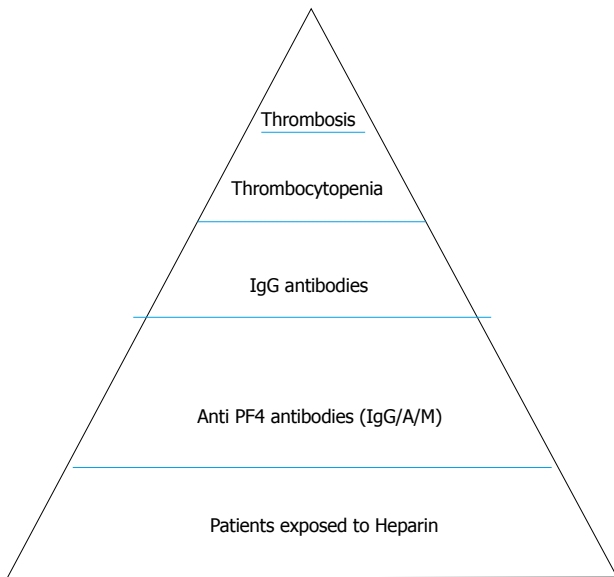


Figure 1 Iceberg model for heparin induced thrombocytopenia syndrome as proposed by Warkentin *et al*^[37]. The size of various iceberg sections and the portion seen, can vary in proportion to the other sections depending on the population of patients, preparation of heparin used, *etc.*

facts: (1) heparin-PF4 antibodies can exist naturally in people unexposed to heparin in the past^[36]; (2) only IgG subclass of antibodies are pathological. Hence assays which are not IgG specific are likely to yield a higher false positive result; (3) out of the patients who are anti heparin/PF4IgG positive, only a minority will be positive by the "Gold Standard" platelet activation assays; (4) not all patients with platelet activating antibodies develop the clinical syndrome of HITS; and (5) fraction of the patients with heparin/PF4 antibody depends on the patient population and the type of heparin preparation used.

The above phenomena observed have been conceptualized as an "iceberg model" by Warkentin *et al*^[37], and highlight the fact that HITS is a clinicopathological syndrome rather than just a laboratory diagnosis (Figure 1).

The diagnosis of HITS centers around the pretest probability of HITS being the cause of the drop in platelet count and/or the thrombotic phenomenon observed. In light of this the "4-T's" scoring system was introduced (Table 1)^[38]. Low pretest probability score ruled out HITS in all but one of the 119 patients studied.

Patients with intermediate or high pre-test probability of HITS should be investigated further with enzyme linked immunosorbent assay (ELISA) based methods^[12].

These assays use heparin-PF4 or polyvinyl sulfate-PF4 immobilised onto microtiter plates as antigens. Antibodies in the patient's plasma bind to these antigens and is detected using goat anti human IgG/A/M bound to alkaline phosphatase. Substrate, subsequently added, changes colour in presence of the enzyme. The intensity of the colour change is measured as optical density (OD)

and is directly proportional to the concentration of the antibodies^[39]. Even though these tests are very sensitive (negative predictive values of close to 100%), they tend to yield a high number of false positive results for HITS, depending on the manufacturer of the assay kit and the clinical population. Higher rates of false positive ELISAs are noted in patients post cardiac surgery and those with antiphospholipid antibody (APLA) syndrome. Anti PF4 antibodies rather than anti PF4/heparin antibodies are responsible for false positive ELISA in sera with APLA syndrome^[40].

Following measures may be taken to increase the specificity of ELISA based assays (Table 2): (1) using IgG specific assays: As IgG antibodies are pathogenic, using specific assays targeting IgG antibodies rather than non-specific assays improves the specificity of the test without sacrificing the sensitivity of the assay; (2) using higher OD cut offs: As higher titers of antibodies are associated with a greater probability of HITS, using higher cutoff values (for example 1.0 instead of 0.4) might increase the specificity of the assay. However, this comes at cost of sacrificing sensitivity of the assay; and (3) confirmatory step using high concentration of heparin: As heparin and anti heparin-PF4 antibodies have a stoichiometric relationship, re-performing the ELISA test with higher concentrations of heparin may confirm the presence of anti heparin-PF4 antibodies. However, this approach requires the test to be performed twice, increasing the cost and the turn around time. It can also be falsely negative if the titre of the antibodies is very high.

Diagnosis of HITS should be confirmed with functional platelet assays in patients with intermediate pretest probability and positive ELISA or in patients with high pretest probability with negative ELISA (Figure 2).

Selection of platelet donors can be potentially critical for these assays as certain polymorphisms on the FcγRIIa receptors affects the response of platelets to the activating monoclonal antibodies^[41].

Serotonin release assay (SRA) is the gold standard test for diagnosis of HITS. It utilizes washed donor platelets incubated with ¹⁴C-labelled serotonin. It is considered positive when more than 20% serotonin is released at therapeutic heparin concentrations (0.1-0.3 IU/mL), but not at supra-therapeutic heparin levels (10-100 IU/mL)^[42]. In Australia, out of 675 SRAs requested to the only centre performing this assay between 2010-2012, around 19% were positive for HITS. Interestingly, amongst cases in which 4T score was available, almost 96% had intermediate or high probability 4T score^[43].

Whole blood impedance aggregometry (WBIA) is emerging as a useful alternative to SRA with faster turnaround time (around 15 min), does not use washed platelets and no radioactive waste products. The laboratories running this assay still need access to high reactive platelet donors as using less responsive platelet donors might result in false negative WBIA. The agreement of WBIA with SRA improves if a higher cut

Table 1 4T score as studied by Lo *et al*^[38]

Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)			
	2	1	0
Thrombocytopenia	> 50% fall or platelet nadir $\geq 20 \times 10^9/L$	30%-50% fall or platelet count $10-19 \times 10^9/L$	Fall < 30% or platelet nadir $< 10 \times 10^9/L$
Timing of fall in platelet count	Clear onset between day 5-10 ¹ ; or less than 1 d (if history of heparin exposure within 30 d)	Consistent with d 5-10 fall, but not clear (<i>e.g.</i> , missing platelet counts) or onset of thrombocytopenia after d10 or fall ≤ 1 d (prior heparin exposure 30-100 d ago)	Platelet count fall < 4 d without recent heparin exposure
Thrombosis or other sequelae (<i>e.g.</i> , Skin lesions)	New thrombosis; skin necrosis; acute systemic reaction post unfractionated heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause of thrombocytopenia	None apparent	Possible other cause is evident	Definite
4T score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low			

¹5-10 d after exposure to heparin or low molecular weight heparin.

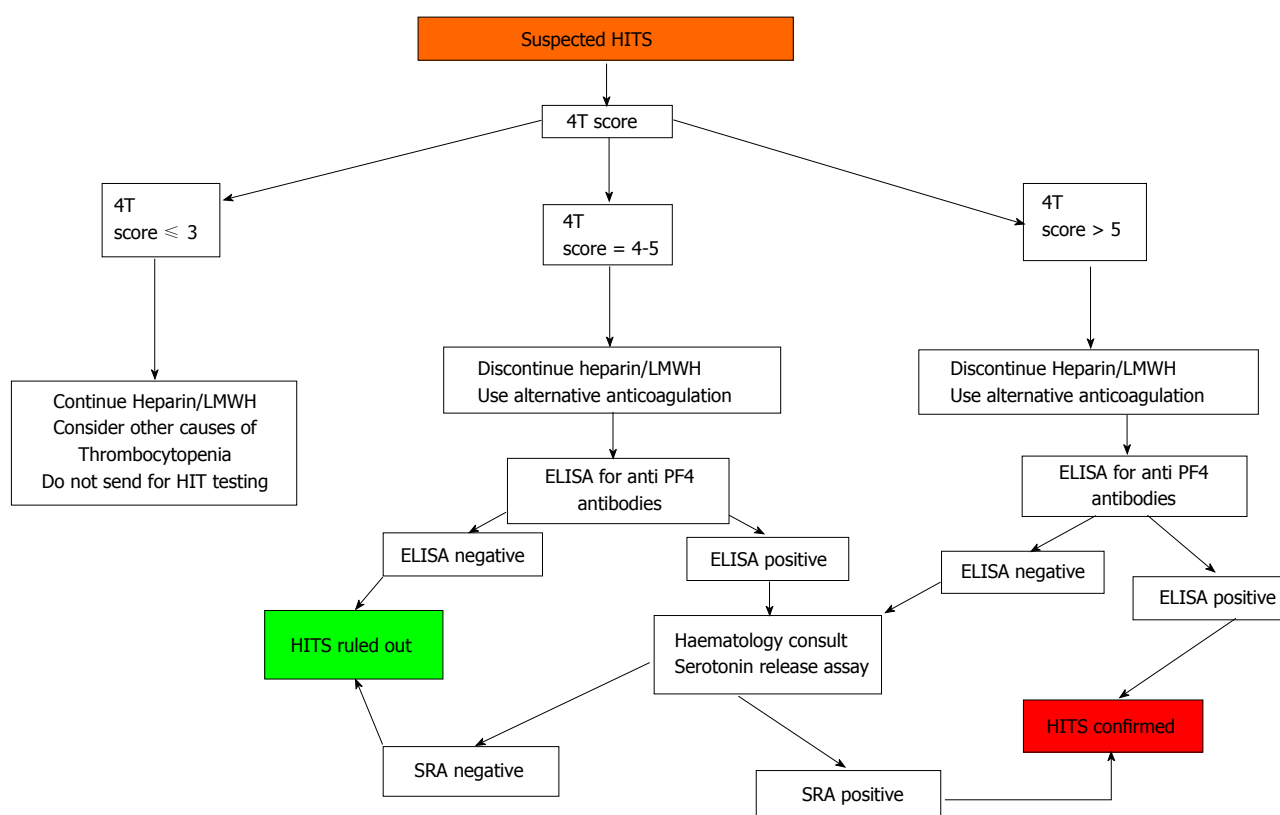


Figure 2 Diagnostic algorithm for Heparin induced thrombocytopenia syndrome. Note that Confirmatory assays for HITS should be considered on the basis of pre test probability rather than ELISA alone. HITS: Heparin induced thrombocytopenia syndrome; SRA : Serotonin release assay. ELISA : Enzyme linked immunosorbent assay.

off of 50% instead of 20%, and if a high dose heparin confirmatory step is used^[44].

TREATMENT

Once a presumptive diagnosis of HITS is made on the basis of pretest probability and anti PF4 antibody assays, therapeutic dosing of alternative anticoagulant is needed along with cessation of the offending agent. Patients are hypercoagulable for days to even weeks despite normalization of platelet counts^[11]. Hence, patients may need to be transitioned to oral anticoagulants once

platelet counts have normalized.

Ideal anticoagulant for treatment of HITS should have following characteristics: (1) should have no risk of generating HITS antibodies; (2) should have robust evidence supporting its use in HITS; (3) should be able to provide predictable anticoagulation and be able to be monitored by an widely available assay; (4) should have short half life; (5) should be easily reversible by an antidote which is readily available; (6) should have a low risk of bleeding and other adverse effects; (7) metabolism and elimination should be reliable and independent of renal or hepatic dysfunction; (8)

Table 2 Characteristics of various assays for heparin induced thrombocytopenia syndrome

	4T score ≤ 3 ^[73-76]	ELISA ^[77]	IgG specific ELISA ^[77]	OD cut off ≥ 1.0 ^[78]	Heparin confirmation step for IgG specific ELISA ^[79]	Serotonin release assay ^[80]	Whole blood impedance Aggregometry ^[44]
Sensitivity	-	100%	100%	80%	94%	100%	90.3%-93.6%
Specificity	-	81%	89%	85%	90%-93%	95%-97%	89%-96%
PPV	-	28%	40%	42%	45%	NA	84.4%-94.8%
NPV	100%	100%	100%	84%	99.50%	NA	-

PPV: Positive predictive value; NPV: Negative predictive value; NA: Not applicable as serotonin release assay is the gold standard assay for diagnosis of heparin induced thrombocytopenia syndrome.

Table 3 Characteristics of alternative anticoagulants

Drug	Route of elimination	Plasma half life	Monitoring	Interaction of antibodies with HITS antibodies	Antidote
Lepirudin	Renal	60 min, up to 200 h in anuric patients ^[81,82]	aPTT (1.5-2 times baseline) ACT on CPB ECT (Not affected by presence of VKAs or UFH)	None	None ?Haemofiltration ^[47]
Desirudin	Renal	2-3 h	None	None	None
Danaparoid	Renal	24 h	Anti-Xa activity (0.5-0.8 U/mL)	Possible, but very rare	None
Argatroban	Hepatic	40-50 min	aPTT (1.5-3 times baseline) ACT on CPB	None	None
Bivalirudin	Enzymatic 80% (Thrombin), renal 20%	25 min	aPTT (1.5-2.5 times baseline) ACT on CPB	None	None ?Haemofiltration ^[52]
Fondaparinux	Renal	17-20 h	None, Anti Xa levels with renal impairment	Case reports only ^[45,61,62]	None

aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; ECT: Ecarin clotting time; CPB: Cardiopulmonary bypass; HITS: Heparin induced thrombocytopenia syndrome; UFH: Unfractionated heparin.

should be safe to use in special subgroup of patients such as those who are pregnant or need to go on to cardiopulmonary bypass; and (9) should be easily available in both oral and intravenous preparations for easy transition between short and longer term anticoagulation.

Unfortunately, such an anticoagulant doesn't exist. Most of the problems from anticoagulation in HITS arise because of the lack of familiarity with non-heparin anticoagulants.

Following are the different categories of anticoagulants which can be used for HITS, based on the clinical scenario (Tables 3 and 4): (1) direct thrombin Inhibitors: Univalent direct thrombin inhibitors (argatroban; dabigatran), bivalent direct thrombin inhibitors [recombinant hirudins (lepirudin, desirudin); synthetic hirudin (bivalirudin)]; and (2) factor Xa antagonists: danaparoid, fondaparinux, rivaroxaban, apixaban.

DIRECT THROMBIN INHIBITORS

Lepirudin

A recombinant hirudin derived from yeast cells, Lepirudin was the first drug approved by United States Food and Drug Administration, for the treatment of HITS in 1998. Even though it reduced new thromboembolic manifestations, it increased the risk of major bleeding

in a combined analysis of 3 prospective trials with historical controls^[45].

Retreatment with lepirudin can increase the risk of anaphylaxis almost half the patients will develop antibodies to lepirudin on initial use. The risk of antibody formation can be reduced by avoiding the bolus and reducing the duration of infusion as much as possible^[46].

Although no antidote is available, use of activated Factor VII to control bleeding and haemofiltration has been described^[47,48].

Argatroban

Argatroban is a synthetic L-arginine derivative, which is tolerated well by patients with moderate renal dysfunction^[49].

Even though the half life is short and use in mild to moderate renal dysfunction is safe, rebound hypercoagulability after cessation of infusion, and spurious prolongation of Prothrombin time when given with warfarin are significant issues, especially when transitioning to longer term oral anticoagulation.

A severity of illness based dosing regime for continuous renal replacement therapy in critically ill is available but not validated^[50].

Bivalirudin

Bivalirudin is a hirudin based synthetic direct thrombin

Table 4 Dosage and availability of anticoagulation agents for heparin induced thrombocytopenia syndrome

Drug	Bolus	Dosage	Dosage in renal impairment	Dosage in hepatic impairment	Availability in Australia
Lepirudin	Only if life or limb threatening thrombosis. 0.4 mg/kg <i>iv</i>	0.1-0.15 mg/kg per hour	Cr. Cl. 45-60: 50% of original infusion rate. Cr. Cl. 30-44: 30% of original infusion rate. Cr. Cl. 15-29: 15% of original infusion rate according to body weight. Avoid if Cr. Cl. Lower or use 0.005 mg/kg per hour if on haemofiltration	No change	Discontinued
Desirudin	None	15-30 mg <i>sc bd</i> . Limited data	Not recommended given paucity of data	No change	Not available
Danaparoid	IV according to body weight. < 60 kg: 1500 U; 60-75 kg: 2250 U; 75-90 kg: 3000 U; > 90 kg: 3750 U	400 U/h IV × 4 h followed by 300 U/h IV × 4 h followed by 200 U/h <i>iv</i>	Reduce dose by 30% and monitor antiXa activity	No change	Available
Bivalirudin	None	0.15-0.2 mg/kg per minute	Cr. Cl 10-29: 0.06 mg/kg per minute; Cr. Cl < 10: 0.015 mg/kg per minute <i>iv</i>	No change	Available
Fondaparinux	None	< 50 kg: 5 mg <i>sc</i> ; 50-100 kg: 7.5 mg <i>sc</i> ; > 100 kg: 10 mg <i>sc</i>	Cr. Cl 30-50: monitor closely. Cr. Cl < 30: Contraindicated	No change	Available
Argatroban	None	2 mcg/kg per minute <i>iv</i>	No change	0.5 mcg/kg per minute	Not available

Cr. Cl.: Creatinine clearance in mL/min; *sc*: Subcutaneous; *iv*: Intravenous.

inhibitor, which binds to free as well as bound thrombin reversibly. It has the shortest half-life amongst the direct thrombin inhibitors and has higher reversibility as up to 80% is eliminated by enzymatic proteolysis^[51]. Due to better pharmacokinetic profile, this is the agent used most widely in patients needing cardiopulmonary bypass. hemodialysis, haemofiltration or plasmapheresis may be used to reverse its effect, even though the data available for efficacy of these therapies is limited^[52].

Desirudin

Desirudin is a recombinant hirudin and is a bivalent, irreversible direct thrombin inhibitor. There is very limited data about use of Desirudin for HITS. An open label randomized pilot trial comparing Desirudin with Argatroban for HITS (PREVENT-HIT) was closed because of poor accrual^[53,54].

FACTOR XA INHIBITORS

Fondaparinux

Fondaparinux is a sulfated pentasaccharide derivative of heparin which binds to antithrombin, inhibiting factor X^[55]. Even though the frequency of heparin - PF4 antibody is similar to Low molecular weight heparins, Fondaparinux induced antibodies are seldom pathogenic^[56,57].

The risk of bleeding while treating HITS is around 5%. Even though some cases of HITS caused by Fondaparinux have been described in literature, benefits such as ease of administration, predictable pharmacokinetics in patients with normal renal function and lack of effect on aPTT makes it an attractive option in patients in whom benefits outweigh low risk of exacerbation of HITS^[45,58-62].

Danaparoid

Danaparoid, a mixture of low molecular sulphated glycosaminoglycans, Heparan, dermatan and chondroitin sulphate is a factor Xa inhibitor. The requirement for monitoring anti Xa levels in most of the critically ill patients developing HITS and risk of cross reaction with heparin-PF4 antibody (< 10% patients) are the factors which need to be considered before using Danaparoid for HITS^[63].

TRANSITION TO ORAL VITAMIN K ANTAGONISTS

For isolated HITS, alternative anticoagulation with or without transition to oral vitamin K antagonists is recommended for up to 4-6 wk. For HITS associated with thrombosis, switching to warfarin followed by continuation of warfarin therapy for 3 mo is recommended.

Transition to warfarin should only be made once platelet count is > 150000/mcl. Warfarin needs to be overlapped with alternative anticoagulation for at least 5 d and until the INR is in the therapeutic range.

Fondaparinux or Danaparoid may be required for transition of Argatroban to oral vitamin K antagonists due to effect of Argatroban on INR.

SPECIAL PATIENT POPULATIONS

Pregnancy

HITS is extremely rare during pregnancy and all the data regarding diagnosis and management is anecdotal. Thrombocytopenia occurs in 7%-8% pregnancies. Most common reason for thrombocytopenia is gestational (haemodilution, increased platelet aggregation due to

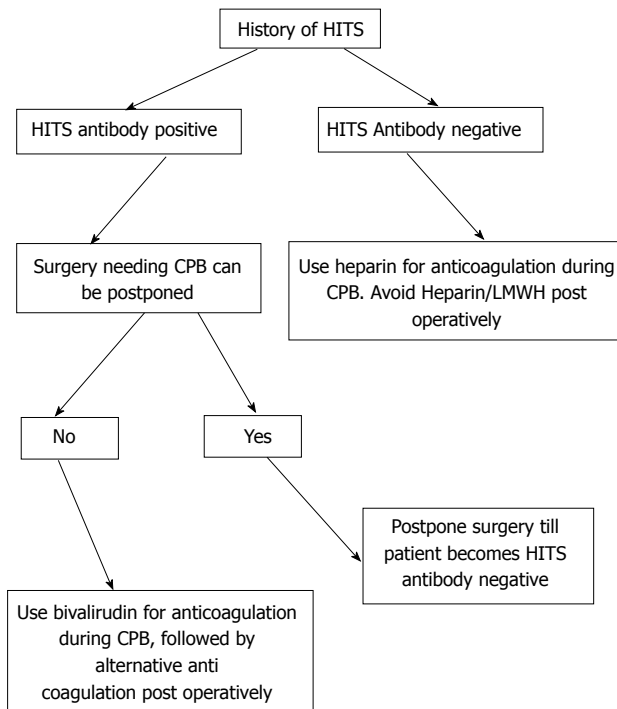


Figure 3 Suggested approach for patients with heparin induced thrombocytopenia syndrome needing cardiopulmonary bypass. HITS: Heparin induced thrombocytopenia syndrome; CPB: Cardiopulmonary bypass.

raised thromboxane A_2 , increased platelet consumption) followed by other causes such as HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, Preeclampsia/eclampsia, acute fatty liver disease of pregnancy, Idiopathic thrombocytopenic purpura, etc.^[64].

In a review of 2777 pregnancies involving exposure to LMWH, none of the patients developed thrombocytopenia attributable to HITS^[65].

Ease of administration, safety in longer term use, and transplacental transfer are special considerations in this group of patients. Despite case reports of the use of argatroban, fondaparinux and danaparoid are preferred because of their subcutaneous administration and availability of large data on longer term use during pregnancy^[66-68].

Cardiopulmonary bypass

Patients with history of HITS that require cardiopulmonary bypass can be managed based on their HITS antibody status (Figure 3).

Bivalirudin is the alternative anticoagulant most well described in literature, however lepirudin and argatroban have also been described^[69-72].

We recommend Bivalirudin for anticoagulation while on cardiopulmonary bypass, as it has been compared directly with heparin in an open label randomized control trial with heparin and protamine reversal. As Bivalirudin is metabolized by thrombin in the blood, care must be taken to avoid any stasis in the venous circuit, surgical field, and the vein grafts. Citrate phosphate

dextrose acetate is used for anticoagulation in the cell saver.

CONCLUSION

The diagnosis of HITS in critically ill patients requires early recognition for successful management. Exclusion of other causes for thrombocytopenia and or thrombosis with special consideration to the temporal relationship of onset of thrombocytopenia with exposure to UFH/LMWH is vital. Use of clinical pretest probability scores such as 4T score in conjunction with more specific assays such as anti-IgG heparin PF4 antibody may reduce over-diagnosis of the disease. Confirmatory tests such as the SRA should be considered for equivocal cases; new tests such as WBIA based assay show promise. Attention to risk of bleeding with invasive interventions, presence and degree of renal/hepatic dysfunction, and availability and cost of alternative anticoagulation agents is important. Finally, patients requiring cardiopulmonary bypass and pregnant patients present rare and challenging scenarios.

REFERENCES

- 1 **Howell W**, Holt E. Two new factors in blood coagulation: heparin and pro-antithrombin. *Am J Physiol* 1918; **47**: 328-341
- 2 **Crafoord C**. Preliminary Report on post operative treatment with heparin as a preventative of thrombosis. *Acta Chirurgica Scand* 1936; **79**: 407-426
- 3 **Weismann RE**, Tobin RW. Arterial embolism occurring during systemic heparin therapy. *AMA Arch Surg* 1958; **76**: 219-225; discussion 225-227 [PMID: 13497418 DOI: 10.1001/archsurg.1958.01280200041005]
- 4 **Roberts B**, Rosato FE, Rosato EF. Heparin--a cause of arterial emboli? *Surgery* 1964; **55**: 803-808 [PMID: 14168000]
- 5 **Natelson EA**, Lynch EC, Alfrey CP, Gross JB. Heparin-induced thrombocytopenia. An unexpected response to treatment of consumption coagulopathy. *Ann Intern Med* 1969; **71**: 1121-1125 [PMID: 5391254 DOI: 10.7326/0003-4819-71-6-1121]
- 6 **Kelton JG**, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008; **112**: 2607-2616 [PMID: 18809774 DOI: 10.1182/blood-2008-02-078014]
- 7 **Rhodes GR**, Dixon RH, Silver D. Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations. *Surg Gynecol Obstet* 1973; **136**: 409-416 [PMID: 4688805]
- 8 **Priziola JL**, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. *Crit Care Med* 2010; **38**: S145-S154 [PMID: 20502168 DOI: 10.1097/CCM.0b013e3181de0b88]
- 9 **Moreau D**, Timsit JF, Vesin A, Garrouste-Orgeas M, de Lassence A, Zahar JR, Adrie C, Vincent F, Cohen Y, Schlemmer B, Azoulay E. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. *Chest* 2007; **131**: 1735-1741 [PMID: 17475637 DOI: 10.1378/chest.06-2233]
- 10 **Ortel TL**. Acquired thrombotic risk factors in the critical care setting. *Crit Care Med* 2010; **38**: S43-S50 [PMID: 20083913 DOI: 10.1097/CCM.0b013e3181e9ccc8]
- 11 **Girolami B**, Prandoni P, Stefani PM, Tanduo C, Sabbion P, Eichler P, Ramon R, Baggio G, Fabris F, Girolami A. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood* 2003; **101**: 2955-2959 [PMID: 12480713 DOI: 10.1182/blood-2002-07-2201]
- 12 **Arepally GM**, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355**: 809-817 [PMID:

- 16928996 DOI: 10.1056/NEJMcp052967]
- 13 **Kelton JG**, Sheridan D, Santos A, Smith J, Steeves K, Smith C, Brown C, Murphy WG. Heparin-induced thrombocytopenia: laboratory studies. *Blood* 1988; **72**: 925-930 [PMID: 3416077]
 - 14 **Newman PM**, Chong BH. Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4-heparin antibodies to platelets and the resultant platelet activation. *Blood* 2000; **96**: 182-187 [PMID: 10891449]
 - 15 **Horsewood P**, Hayward CP, Warkentin TE, Kelton JG. Investigation of the mechanisms of monoclonal antibody-induced platelet activation. *Blood* 1991; **78**: 1019-1026 [PMID: 1714324]
 - 16 **Chong BH**, Fawaz I, Chesterman CN, Berndt MC. Heparin-induced thrombocytopenia: mechanism of interaction of the heparin-dependent antibody with platelets. *Br J Haematol* 1989; **73**: 235-240 [PMID: 2818941 DOI: 10.1111/j.1365-2141.1989.tb00258.x]
 - 17 **Warkentin TE**, Hayward CP, Boshkov LK, Santos AV, Sheppard JA, Bode AP, Kelton JG. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood* 1994; **84**: 3691-3699 [PMID: 7949124]
 - 18 **Warkentin TE**, Sheppard JI. Generation of platelet-derived microparticles and procoagulant activity by heparin-induced thrombocytopenia IgG/serum and other IgG platelet agonists: a comparison with standard platelet agonists. *Platelets* 1999; **10**: 319-326 [PMID: 16801109 DOI: 10.1080/09537109975960]
 - 19 **Cines DB**, Tomaski A, Tannenbaum S. Immune endothelial-cell injury in heparin-associated thrombocytopenia. *N Engl J Med* 1987; **316**: 581-589 [PMID: 3807952 DOI: 10.1056/NEJM198703053161004]
 - 20 **Rauova L**, Hirsch JD, Greene TK, Zhai L, Hayes VM, Kowalska MA, Cines DB, Poncz M. Monocyte-bound PF4 in the pathogenesis of heparin-induced thrombocytopenia. *Blood* 2010; **116**: 5021-5031 [PMID: 20724543 DOI: 10.1182/blood-2010-03-27694]
 - 21 **Kowalska MA**, Krishnaswamy S, Rauova L, Zhai L, Hayes V, Amirikian K, Esko JD, Bougie DW, Aster RH, Cines DB, Poncz M. Antibodies associated with heparin-induced thrombocytopenia (HIT) inhibit activated protein C generation: new insights into the prothrombotic nature of HIT. *Blood* 2011; **118**: 2882-2888 [PMID: 21772054 DOI: 10.1182/blood-2011-02-335208]
 - 22 **Warkentin TE**. HIT paradigms and paradoxes. *J Thromb Haemost* 2011; **9** Suppl 1: 105-117 [PMID: 21781246 DOI: 10.1111/j.1538-7836.2011.04322.x]
 - 23 **Jaax ME**, Krauel K, Marschall T, Brandt S, Gansler J, Füll B, Appel B, Fischer S, Block S, Helm CA, Müller S, Preissner KT, Greinacher A. Complex formation with nucleic acids and aptamers alters the antigenic properties of platelet factor 4. *Blood* 2013; **122**: 272-281 [PMID: 23673861 DOI: 10.1016/j.cimid.2013.04.001]
 - 24 **Warkentin TE**, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, Kelton JG. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332**: 1330-1335 [PMID: 7715641 DOI: 10.1056/NEJM199505183322003]
 - 25 **Cuker A**. Recent advances in heparin-induced thrombocytopenia. *Curr Opin Hematol* 2011; **18**: 315-322 [PMID: 21730833 DOI: 10.1097/MOH.0b013e3283497ef2]
 - 26 **Selleng K**, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med* 2007; **35**: 1165-1176 [PMID: 17334253 DOI: 10.1097/01.CCM.0000259538.02375.A5]
 - 27 **Warkentin TE**, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood* 2006; **108**: 2937-2941 [PMID: 16857993 DOI: 10.1182/blood-2005-11-012450]
 - 28 **Warkentin TE**, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood* 2000; **96**: 1703-1708 [PMID: 10961867]
 - 29 **Lubenow N**, Hinz P, Thomaschewski S, Lietz T, Vogler M, Ladwig A, Jünger M, Nauck M, Schellong S, Wander K, Engel G, Ekkernkamp A, Greinacher A. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. *Blood* 2010; **115**: 1797-1803 [PMID: 19965682 DOI: 10.1182/blood-2009-07-231506]
 - 30 **Warkentin TE**, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; **344**: 1286-1292 [PMID: 11320387 DOI: 10.1056/NEJM200104263441704]
 - 31 **Gruel Y**, Pouplard C. Post-operative platelet count profile: the most reliable tool for identifying patients with true heparin-induced thrombocytopenia after cardiac surgery. *J Thromb Haemost* 2010; **8**: 27-29 [PMID: 19817999 DOI: 10.1111/j.1538-7836.2009.03646.x]
 - 32 **Zwicker JI**, Uhl L, Huang WY, Shaz BH, Bauer KA. Thrombosis and ELISA optical density values in hospitalized patients with heparin-induced thrombocytopenia. *J Thromb Haemost* 2004; **2**: 2133-2137 [PMID: 15613017 DOI: 10.1111/j.1538-7836.2004.01039.x]
 - 33 **Warkentin TE**, Greinacher A. Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes. *Expert Opin Drug Saf* 2009; **8**: 129-144 [PMID: 19309242 DOI: 10.1517/14740330902778180]
 - 34 **Schindewolf M**, Kroll H, Ackermann H, Garbaraviciene J, Kaufmann R, Boehncke WH, Ludwig RJ, Lindhoff-Last E. Heparin-induced non-necrotizing skin lesions: rarely associated with heparin-induced thrombocytopenia. *J Thromb Haemost* 2010; **8**: 1486-1491 [PMID: 20128858 DOI: 10.1111/j.1538-7836.2010.03795.x]
 - 35 **Teh CH**, Robertson MN, Warkentin TE, Henriksen PA, Brackenbury ET, Anderson JA. Transient global amnesia as the presenting feature of heparin-induced thrombocytopenia. *J Card Surg* 2010; **25**: 300-302 [PMID: 20202039 DOI: 10.1111/j.1540-8191.2010.01007.x]
 - 36 **Greinacher A**, Holtfrete B, Krauel K, Gätke D, Weber C, Ittermann T, Hammerschmidt S, Kocher T. Association of natural anti-platelet factor 4/heparin antibodies with periodontal disease. *Blood* 2011; **118**: 1395-1401 [PMID: 21659541 DOI: 10.1182/blood-2011-03-342857]
 - 37 **Warkentin TE**. Heparin-induced thrombocytopenia: pathogenesis and management. *Br J Haematol* 2003; **121**: 535-555 [PMID: 12752095 DOI: 10.1046/j.1365-2141.2003.04334.x]
 - 38 **Lo GK**, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006; **4**: 759-765 [PMID: 16634744 DOI: 10.1111/j.1538-7836.2006.01787.x]
 - 39 **Otis SA**, Zehnder JL. Heparin-induced thrombocytopenia: current status and diagnostic challenges. *Am J Hematol* 2010; **85**: 700-706 [PMID: 20665476 DOI: 10.1002/ajh.21770]
 - 40 **Paunzer R**, Greinacher A, Selleng K, Althaus K, Shenkman B, Seligsohn U. False-positive tests for heparin-induced thrombocytopenia in patients with antiphospholipid syndrome and systemic lupus erythematosus. *J Thromb Haemost* 2009; **7**: 1070-1074 [PMID: 19291166 DOI: 10.1111/j.1538-7836.2009.03335.x]
 - 41 **Tan CW**, Ward CM, Morel-Kopp MC. Evaluating heparin-induced thrombocytopenia: the old and the new. *Semin Thromb Hemost* 2012; **38**: 135-143 [PMID: 22422328 DOI: 10.1055/s-0032-1301411]
 - 42 **Sheridan D**, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. *Blood* 1986; **67**: 27-30 [PMID: 3940551]
 - 43 **Just S**, Brighton T. Review of SRA results for confirmation of Heparin Induced Thrombotic Thrombocytopenia (HITT). *HAA* 2013: Abstract
 - 44 **Morel-Kopp MC**, Tan CW, Brighton TA, McRae S, Baker R, Tran H, Mollee P, Kershaw G, Joseph J, Ward C. Validation of whole blood impedance aggregometry as a new diagnostic tool for HIT: results of a large Australian study. *Thromb Haemost* 2012; **107**: 575-583 [PMID: 22234599 DOI: 10.1160/TH11-09-0631]
 - 45 **Pistulli R**, Oberle V, Figulla HR, Yilmaz A, Pfeifer R. Fondaparinux cross-reacts with heparin antibodies in vitro in a patient with fondaparinux-related thrombocytopenia. *Blood Coagul Fibrinolysis* 2011; **22**: 76-78 [PMID: 21076279 DOI: 10.1097/MBC.0b013e328340ff24]

- 46 **Greinacher A**, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003; **108**: 2062-2065 [PMID: 14568897 DOI: 10.1161/01.CIR.0000096056.37269.14]
- 47 **Mon C**, Moreno G, Ortiz M, Diaz R, Herrero JC, Olié A, Rodriguez I, Ortega O, Gallar P, Vigil A. Treatment of hirudin overdosage in a dialysis patient with heparin-induced thrombocytopenia with mixed hemodialysis and hemofiltration treatment. *Clin Nephrol* 2006; **66**: 302-305 [PMID: 17063999]
- 48 **Oh JJ**, Akers WS, Lewis D, Ramaiah C, Flynn JD. Recombinant factor VIIa for refractory bleeding after cardiac surgery secondary to anticoagulation with the direct thrombin inhibitor lepirudin. *Pharmacotherapy* 2006; **26**: 569-577 [PMID: 16553518 DOI: 10.1592/phco.26.4.576]
- 49 **Hursting MJ**, Jang IK. Impact of renal function on argatroban therapy during percutaneous coronary intervention. *J Thromb Thrombolysis* 2010; **29**: 1-7 [PMID: 19504050 DOI: 10.1007/s11239-009-0357-8]
- 50 **Link A**, Girndt M, Selejan S, Mathes A, Böhm M, Rensing H. Argatroban for anticoagulation in continuous renal replacement therapy. *Crit Care Med* 2009; **37**: 105-110 [PMID: 19050602 DOI: 10.1097/CCM.0b013e3181932394]
- 51 **Sakr Y**. Heparin-induced thrombocytopenia in the ICU: an overview. *Crit Care* 2011; **15**: 211 [PMID: 21457505 DOI: 10.1186/cc9993]
- 52 **Mann MJ**, Tseng E, Ratcliffe M, Strattman G, De Silva A, Demarco T, Achorn N, Moskalik W, Hoopes C. Use of bivalirudin, a direct thrombin inhibitor, and its reversal with modified ultrafiltration during heart transplantation in a patient with heparin-induced thrombocytopenia. *J Heart Lung Transplant* 2005; **24**: 222-225 [PMID: 15701441 DOI: 10.1016/j.healun.2003.11.401]
- 53 **Frame JN**, Rice L, Bartholomew JR, Whelton A. Rationale and design of the PREVENT-HIT study: a randomized, open-label pilot study to compare desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis. *Clin Ther* 2010; **32**: 626-636 [PMID: 20435232 DOI: 10.1016/j.clinthera.2010.04.012]
- 54 **Boyce SW**, Bandyk DF, Bartholomew JR, Frame JN, Rice L. A randomized, open-label pilot study comparing desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis: PREVENT-HIT Study. *Am J Ther* 2011; **18**: 14-22 [PMID: 21079512 DOI: 10.1097/MJT.0b013e3181f65503]
- 55 **Kelton JG**, Arnold DM, Bates SM. Nonheparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med* 2013; **368**: 737-744 [PMID: 23425166 DOI: 10.1056/NEJMc1206642]
- 56 **Pappalardo F**, Scandroglio A, Maj G, Zangrillo A, D'Angelo A. Treatment of heparin-induced thrombocytopenia after cardiac surgery: preliminary experience with fondaparinux. *J Thorac Cardiovasc Surg* 2010; **139**: 790-792 [PMID: 19660283 DOI: 10.1016/j.jtcvs.2008.11.032]
- 57 **Grouzi E**, Kyriakou E, Panagou I, Spiliotopoulou I. Fondaparinux for the treatment of acute heparin-induced thrombocytopenia: a single-center experience. *Clin Appl Thromb Hemost* 2010; **16**: 663-667 [PMID: 19825921 DOI: 10.1177/1076029609347900]
- 58 **Warkentin TE**. Fondaparinux: does it cause HIT? Can it treat HIT? *Expert Rev Hematol* 2010; **3**: 567-581 [PMID: 21083474 DOI: 10.1586/ehm.10.54]
- 59 **Warkentin TE**, Davidson BL, Büller HR, Gallus A, Gent M, Lensing AW, Piovella F, Prins MH, Segers AE, Kelton JG. Prevalence and risk of preexisting heparin-induced thrombocytopenia antibodies in patients with acute VTE. *Chest* 2011; **140**: 366-373 [PMID: 21393394 DOI: 10.1378/chest.10-1599]
- 60 **Warkentin TE**, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. *N Engl J Med* 2007; **356**: 2653-2655; discussion 2653-2655 [PMID: 17582083 DOI: 10.1056/NEJMc070346]
- 61 **Rota E**, Bazzan M, Fantino G. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin (LMWH)-induced heparin-induced thrombocytopenia (HIT). *Thromb Haemost* 2008; **99**: 779-781 [PMID: 18392338 DOI: 10.1160/TH07-09-0573]
- 62 **Salem M**, Elrefai S, Shrit MA, Warkentin TE. Fondaparinux thromboprophylaxis-associated heparin-induced thrombocytopenia syndrome complicated by arterial thrombotic stroke. *Thromb Haemost* 2010; **104**: 1071-1072 [PMID: 20806120 DOI: 10.1160/TH10-05-0284]
- 63 **Tardy-Poncet B**, Wolf M, Lasne D, Bauters A, Ffrench P, Elalami I, Tardy B. Danaparoid cross-reactivity with heparin-induced thrombocytopenia antibodies: report of 12 cases. *Intensive Care Med* 2009; **35**: 1449-1453 [PMID: 19350215 DOI: 10.1007/s00134-009-1464-x]
- 64 **Berkley E**, Kilpatrick SJ. Thrombocytopenia in pregnancy: making the differential diagnosis. *Contemporary OB/GYN* 2009; **54**: 36-38
- 65 **Greer IA**, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005; **106**: 401-407 [PMID: 15811953 DOI: 10.1182/blood-2005-02-0626]
- 66 **Knol HM**, Schultinge L, Erwich JJ, Meijer K. Fondaparinux as an alternative anticoagulant therapy during pregnancy. *J Thromb Haemost* 2010; **8**: 1876-1879 [PMID: 20492464 DOI: 10.1111/j.1538-7836.2010.03926.x]
- 67 **Nagler M**, Haslauer M, Willemin WA. Fondaparinux - data on efficacy and safety in special situations. *Thromb Res* 2012; **129**: 407-417 [PMID: 22133273 DOI: 10.1016/j.thromres.2011.10.037]
- 68 **Lindhoff-Last E**, Kreutzenbeck HJ, Magnani HN. Treatment of 51 pregnancies with danaparoid because of heparin intolerance. *Thromb Haemost* 2005; **93**: 63-69 [PMID: 15630492 DOI: 10.1160/TH04-06-0345]
- 69 **Dyke CM**, Koster A, Veale JJ, Maier GW, McNiff T, Levy JH. Preemptive use of bivalirudin for urgent on-pump coronary artery bypass grafting in patients with potential heparin-induced thrombocytopenia. *Ann Thorac Surg* 2005; **80**: 299-303 [PMID: 15975385 DOI: 10.1016/j.athoracsur.2004.08.037]
- 70 **Dyke CM**, Smedira NG, Koster A, Aronson S, McCarthy HL, Kirshner R, Lincoff AM, Spiess BD. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. *J Thorac Cardiovasc Surg* 2006; **131**: 533-539 [PMID: 16515902 DOI: 10.1016/j.jtcvs.2005.09.057]
- 71 **Koster A**, Hansen R, Kuppe H, Hetzer R, Crystal GJ, Mertzluft F. Recombinant hirudin as an alternative for anticoagulation during cardiopulmonary bypass in patients with heparin-induced thrombocytopenia type II: a 1-year experience in 57 patients. *J Cardiothorac Vasc Anesth* 2000; **14**: 243-248 [PMID: 10890473 DOI: 10.1053/cr.2000.5861]
- 72 **Martin ME**, Kloecker GH, Laber DA. Argatroban for anticoagulation during cardiac surgery. *Eur J Haematol* 2007; **78**: 161-166 [PMID: 17328717 DOI: 10.1111/j.1600-0609.2006.00786]
- 73 **Pouplard C**, Gueret P, Fouassier M, Temisien C, Trossaert M, Régina S, Gruel Y. Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost* 2007; **5**: 1373-1379 [PMID: 17362241 DOI: 10.1111/j.1538-7836.2007.02524.x]
- 74 **Crowther MA**, Cook DJ, Albert M, Williamson D, Meade M, Granton J, Skrobik Y, Langevin S, Mehta S, Hebert P, Guyatt GH, Geerts W, Rabbat C, Douketis J, Zytaruk N, Sheppard J, Greinacher A, Warkentin TE. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care* 2010; **25**: 287-293 [PMID: 20149589 DOI: 10.1016/j.jrc.2009.12.006]
- 75 **Bryant A**, Low J, Austin S, Joseph JE. Timely diagnosis and management of heparin-induced thrombocytopenia in a frequent request, low incidence single centre using clinical 4T's score and particle gel immunoassay. *Br J Haematol* 2008; **143**: 721-726 [PMID: 19036016 DOI: 10.1111/j.1365-2141.2008.07401.x]
- 76 **Demma LJ**, Winkler AM, Levy JH. A diagnosis of heparin-induced thrombocytopenia with combined clinical and laboratory methods in cardiothoracic surgical intensive care unit patients. *Anesth Analg* 2011; **113**: 697-702 [PMID: 21788317 DOI: 10.1213/

- ANE.0b013e3182297031]
- 77 **Bakchoul T**, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. Prospective evaluation of PF4/heparin immunoassays for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost* 2009; **7**: 1260-1265 [PMID: 19422442 DOI: 10.1111/j.1538-7836.2009.03465.x]
 - 78 **Ruf KM**, Bensadoun ES, Davis GA, Flynn JD, Lewis DA. A clinical-laboratory algorithm incorporating optical density value to predict heparin-induced thrombocytopenia. *Thromb Haemost* 2011; **105**: 553-559 [PMID: 21264443 DOI: 10.1160/TH10-09-0610]
 - 79 **Bakchoul T**, Giptner A, Bein G, Santoso S, Sachs UJ. Performance characteristics of two commercially available IgG-specific immunoassays in the assessment of heparin-induced thrombocytopenia (HIT). *Thromb Res* 2011; **127**: 345-348 [PMID: 21232785 DOI: 10.1016/j.thromres.2010.12.001]
 - 80 **Warkentin TE**, Sheppard JA, Moore JC, Moore KM, Sigouin CS, Kelton JG. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? *J Lab Clin Med* 2005; **146**: 341-346 [PMID: 16310517 DOI: 10.1016/j.lab.2005.08.003]
 - 81 **Vanholder R**, Camez A, Veys N, Van Loo A, Dhondt AM, Ringoir S. Pharmacokinetics of recombinant hirudin in hemodialyzed end-stage renal failure patients. *Thromb Haemost* 1997; **77**: 650-655 [PMID: 9134637]
 - 82 **Eichler P**, Friesen HJ, Lubenow N, Jaeger B, Greinacher A. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. *Blood* 2000; **96**: 2373-2378 [PMID: 11001886]

P- Reviewer: De Cristofaro R, Kadusevicius E, Puddu PE

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu HL



Steps to consider in the approach and management of critically ill patient with spontaneous intracerebral hemorrhage

Daniel Agustin Godoy, Gustavo Rene Piñero, Patricia Koller, Luca Masotti, Mario Di Napoli

Daniel Agustin Godoy, Neurocritical Care Unit, Sanatorio Pasteur, Catamarca 4700, Argentina

Daniel Agustin Godoy, Intensive Care Unit, San Juan Bautista Hospital, Catamarca 4700, Argentina

Gustavo Rene Piñero, Patricia Koller, Intensive Care Unit, Leónidas Lucero Hospital, Bahía Blanca, Buenos Aires 1427, Argentina

Luca Masotti, Internal Medicine, Santa Maria Nuova Hospital, 50134 Florence, Italy

Mario Di Napoli, Neurological Service, San Camillo de' Lellis General Hospital, 02100 Rieti, Italy

Mario Di Napoli, Neurological Section, SMDN-Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention, 67039 Sulmona, L'Aquila, Italy

Author contributions: Godoy DA designed research; Piñero GR, Koller P and Masotti L performed research; Godoy DA and Di Napoli M analyzed data; Godoy DA and Di Napoli M wrote the paper.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Daniel Agustin Godoy, Neurocritical Care Unit, Sanatorio Pasteur, Chacabuco 675, Catamarca 4700, Argentina. dagodoytorres@yahoo.com.ar
Telephone: +54-38-34432005
Fax: +54-38-34432006

Received: November 8, 2014

Peer-review started: November 9, 2014

First decision: December 26, 2014

Revised: March 3, 2015

Accepted: June 4, 2015

Article in press: June 8, 2015

Published online: August 4, 2015

Abstract

Spontaneous intracerebral hemorrhage is a type of stroke associated with poor outcomes. Mortality is elevated, especially in the acute phase. From a pathophysiological point of view the bleeding must traverse different stages dominated by the possibility of re-bleeding, edema, intracranial hypertension, inflammation and neurotoxicity due to blood degradation products, mainly hemoglobin and thrombin. Neurological deterioration and death are common in early hours, so it is a true neurological-neurosurgical emergency. Time is brain so that action should be taken fast and accurately. The most significant prognostic factors are level of consciousness, location, volume and ventricular extension of the bleeding. Nihilism and early withdrawal of active therapy undoubtedly influence the final result. Although there are no proven therapeutic measures, treatment should be individualized and guided preferably by pathophysiology. The multidisciplinary teamwork is essential. Results of recently completed studies have birth to promising new strategies. For correct management it's important to establish an orderly and systematic strategy based on clinical stabilization, evaluation and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies, including hemostatic therapy and intensive control of elevated blood pressure. Uncertainty continues regarding the role of surgery.

Key words: Intracerebral hemorrhage; Prognosis; Hematoma expansion; Inflammation; Hemostatic therapy; Oral anticoagulants

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Spontaneous intracerebral hemorrhage is associated with poor outcome. Neurological deterioration and death are common in early hours, so it is a true neurological-neurosurgical emergency. Nihilism and early withdrawal of active therapy clearly influence the outcome. Action should be taken fast and accurately. Treatment should be individualized and guided preferably by pathophysiology in a multidisciplinary team work. For correct management it's important to establish an orderly and systematic strategy based on clinical stabilization, evaluation and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies, including hemostatic therapy and intensive control of elevated blood pressure.

Godoy DA, Piñero GR, Koller P, Masotti L, Di Napoli M. Steps to consider in the approach and management of critically ill patient with spontaneous intracerebral hemorrhage. *World J Crit Care Med* 2015; 4(3): 213-229 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/213.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.213>

INTRODUCTION

Intracerebral hemorrhage (ICH) is defined as the spontaneous extravasation of blood into the brain parenchyma with or without extension of bleeding into subarachnoid or intraventricular spaces^[1-4]. ICH account for 10% to 30% of all stroke-hospital admissions^[1-4], and is one of the most devastating forms of stroke. Its estimated incidence is between 12 and 15 cases per 100000 inhabitants per year. Arterial hypertension and oral anticoagulants are the major risk factors^[1-4]. The clinical presentation is characterized by a rapidly deteriorating neurological status coupled with signs and symptoms of elevated intracranial pressure^[1-5]. The diagnosis is established by the use of neuroimaging [computed tomography (CT) scan or magnetic resonance imaging (MRI)]^[1-5]. The mortality rate is averaging 50%, most of which occur during the first 5 d^[1-5]. Only one-third of the survivors resume his life prior to the event^[1-5]. Unfortunately, there is no proven specific treatment; however, a comprehensive and multidisciplinary approach based on pathophysiology helps to achieve favorable results^[1-5]. The main objective of this manuscript is to review all aspects of spontaneous ICH, with emphasis on its pathophysiology with the intention to suggest steps to consider for the management of this lethal entity (Figure 1).

TO DELETE NIHILISM AND SELF-FULFILLING PROPHECIES

Nihilism (from the Latin nihil, "nothing") is the philosophical principle that is based on the negation of one or more of the supposed meanings of life. Nietzsche indicates that denial or disbelief in anything are the results of doubt and disorientation^[6]. The nihilism has dominated the scene of spontaneous ICH for many years, perhaps due to the absence of specific therapies. One of the most important determinants of the outcome of the individual victims of ICH is the level of support provided. If this support is not adequate or suspended based on beliefs of poor prognosis, it can trigger self-fulfilling prophecies^[7]. As stated by Robert Merton, self-fulfilled prophecies are based on a false conception or belief that eventually triggers a behavior or conduct false that with the time becomes true^[8].

Moreover, in ICH and other brain injuries, orders of do-not-resuscitation (DNR) or withdrawal of support based on self-fulfilled prophecies or nihilism, have a definite influence on mortality^[7,9,10]. Delete nihilistic attitude is indispensable in the management of spontaneous ICH.

These philosophical principles have scientific evidence that supports them. Various studies have highlighted the impact of treating this population of patients in specialized, multidisciplinary units, which increase the probability of survival and good outcome^[11,12]. The reasons remain uncertain, but several factors seem to influence, such as; the absence of nihilistic attitude, decreased stay in intensive care units, a lower incidence of neurological or systemic complications and early discharge to rehabilitation units^[11-13].

TO KNOWN NATURAL HISTORY AND PATHOPHYSIOLOGY OF INTRACEREBRAL HEMORRHAGE

Natural history

Thirty-day mortality of ICH victims is nearly to 50%, most of which occurs during the acute phase^[1-4]. The causes of death vary according to the time course of the disease^[14-16]. Nearly 80% of cases of early death are of neurological origin^[14-16]. About one-fifth of these patients does not reach the hospital and dies due to the magnitude of the primary or initial damage^[17]. The rest of the patients dies by withdrawal of support due to brain death secondary to localization of the bleeding (brainstem); intracranial hypertension due to initial bleeding or as a result of the expansion of the hematoma^[14-16]. The remaining 20% died by cardiac causes^[14-16]. After the first week, death is caused by medical complications, mainly sepsis^[14-16].

One-year mortality varies according to different locations: 51% for deep (thalamic or putaminal), 57% for lobar, 42% for cerebellar and 65% for brain stem

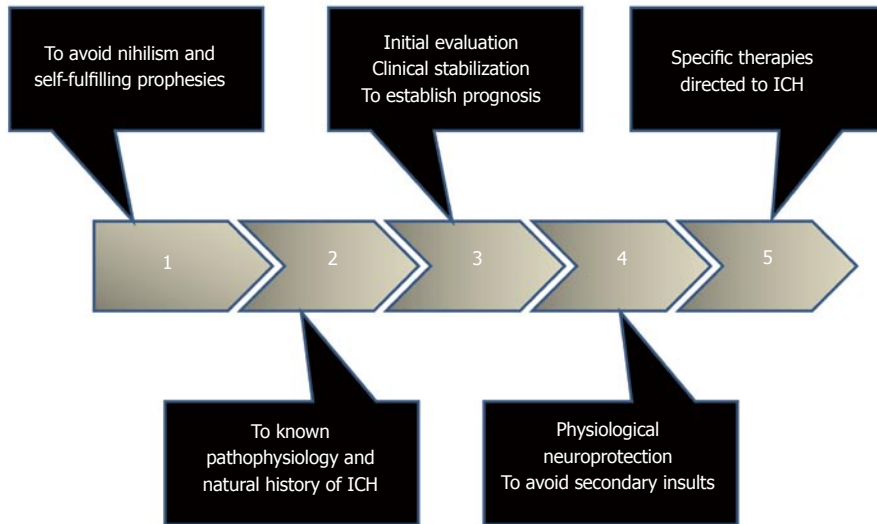


Figure 1 Steps to consider in the approach to the critically ill patient with spontaneous intracerebral hemorrhage. ICH: Intracerebral hemorrhage.

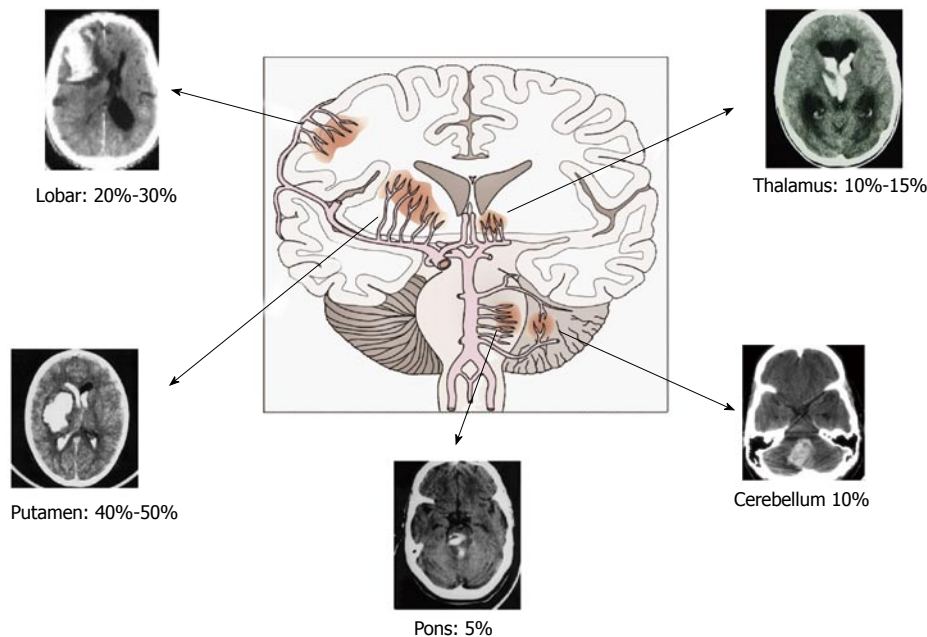


Figure 2 Typical sites of bleeding in spontaneous intracerebral hemorrhage.

hemorrhages, respectively^[1].

Pathophysiology of spontaneous ICH

The events that follow bleeding within the brain parenchyma are varied, complex, simultaneous, and interrelated. For teaching purposes, we will divide them, in different phases^[18].

Vascular rupture: Arterial hypertension is a common risk factor for ICH^[1-5]. Nearly 80% of patients with ICH present arterial hypertension at the admission and most have a history of hypertension^[1,5]. Chronic hypertension imposes constant mechanical stress to cerebral arterioles (60-100 μ in diameter), which triggers hyperplasia of smooth muscle cells^[1-5,19]. Over time,

muscle cells die, are replaced by collagen, weakening the arterial wall, making it prone to stasis, occlusion, and rupture^[19].

The sites at higher risk for these changes are the bifurcations or branches of penetrating arteries, such as lenticulostriate, thalamus and brainstem perforating arteries, thus explaining the most common hematoma locations^[1-5] (Figure 2).

The extent of bleeding is mainly determined by the size of the gap in the arteriolar wall, systemic blood pressure, and hemostatic mechanisms^[19].

Sometimes, the arterioles invaded by collagen develop microscopic dilatations, known as "Charcot-Bouchard aneurysms". These changes can be found in autopsy specimens, but they are not always associated

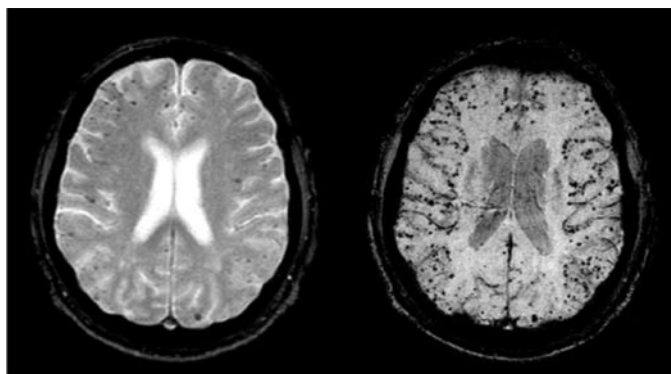


Figure 3 Micro bleeds in magnetic resonance image.

with bleeding sites; therefore, their clinical significance is controversial^[1-5,19].

In non-hypertensive individuals, particularly the elderly, amyloid angiopathy is the substrate of arterial bleeding. It results from the deposition of amyloid protein in the tunica media and adventitia of capillaries, arterioles, cortical and leptomeningeal arteries causing fragility of the vessel wall. These vessels could break spontaneously or for sudden and abrupt blood pressure changes. Distinctive features of this entity are the predilection for lobar regions (especially in the posterior areas of the brain), multifocality, and recurrence^[1-5,19].

Today, attention is directed towards early detection of micro hemorrhages by MRI, because these have been shown to predict higher risk of lobar ICH^[19,20] (Figure 3).

Following vascular rupture, the phase of *hematoma formation* begins, which develops within 60 min of the initial bleeding^[18]. The sudden bleeding into the brain causes mechanical destruction of the parenchyma and may produce mass effect with increased intracranial pressure, distortions and tissue shift with potential herniation and cerebral ischemia^[1-5,19,20]. The bleeding also triggers cell death through necrosis and apoptosis^[18,21]; inflammation^[18,21,22]; and vasogenic edem^[18,21-23].

A substantial proportion of patients has enlargement of the *hematoma* after the initial event. This expansion is often associated with deterioration of neurological status and poor clinical outcomes^[1-5,24-26].

An increase in the volume of the hematoma is seen in 38% of patients during the first three hours post-stroke. In two-thirds of this population, expansion of the hemorrhage is evident in the first hour^[24-26]. Hematoma growth may occur despite the absence of coagulopathy and although knowledge of the mechanisms of expansion remain inconclusive, they seem to involve continuous bleeding from the initial site or additional bleeding from damage to adjacent small vessels causing satellite hemorrhages at the periphery of the clot^[19].

Various risk factors have been associated with hematoma enlargement. Alcohol abuse, irregularly shaped hematomas, low levels of fibrinogen and prothrombin, diabetes mellitus, liver disease, are frequently reporters factors. However, the most consistent is the time elapsed between symptom onset and first

CT scan^[18,24,27,28]. Longer is the time until the first imaging study, lower the probability of detecting this complication.

After the initial 24 h, the next phase is dominated by the development of edema around the hemorrhage. This period reaches its peak on the third day after the first bleeding, and then declines slowly^[18,21,23].

The most severe form of edema is localized around the clot, mainly spread through the white matter. This edema is primarily vasogenic due to alteration of the blood-brain barrier (BBB). Physical destruction damages the BBB and for the synthesis of substances that contributes to damage, such as thrombin and extracellular matrix metalloproteinases^[18,21,23].

Cerebral blood flow and metabolism during intracerebral hemorrhage

After ICH, cerebral blood flow (CBF) changes with a characteristic temporal profile^[29]. Three phases have been described^[29]: (1) phase I: first 48 h. Metabolism and CBF are reduced in a coupled manner. This period is known as "hibernation phase"; (2) phase II or reperfusion phase: between days 2 to 14. CBF and metabolism vary in the whole cerebral parenchyma, with areas of hypo normal and high CBF; and (3) phase III - normalization: starts in the second week after hemorrhage. CBF and metabolism return to normal values, except in the hemorrhagic site.

Multiple factors contribute to CBF alterations: mechanical compression of microvasculature, intracranial hypertension, disruption of cerebral autoregulation, vasoactive substances and inflammation^[29]. Following ICH, CBF decrease, with lowest values in the perihematomal region^[30,31], however in this zone, metabolic activity also decrease, indicating the absence of ischemia^[32-34].

In summary, the available data allow us to confirm that the area around ICH is characterized by a slight decrease in regional cerebral blood flow but this occurs as a result of the concomitant decrease in metabolic demands. Mitochondrial dysfunction might be responsible for the metabolic depression^[35].

Metabolic penumbra

Recent studies of metabolism in perihematomal zone have revealed a remarkable metabolic distress

Table 1 Intracerebral hemorrhage score

Components	Points
GCS score	
3-4	2
5-12	1
13-15	0
ICH volume (cm ³)	
≥30	1
< 30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (yr)	
≥ 80	1
< 80	0
Total ICH score	0-6

GCS: Glasgow coma scale; IVH: Intraventricular hemorrhage; ICH: Intracerebral hemorrhage.

characterized by an increase in the uptake and glucose utilization especially in the first 4 d after hemorrhage^[36]. This metabolic crisis may persist for about one week, and it is not a consequence of ischemia; therefore, we should speak of metabolic penumbra rather than ischemic penumbra^[36].

The other phenomena taking place around the hematoma are inflammation and neurotoxicity^[18,21,22]. Bleeding activates astrocytes and microglia, which in turn stimulate the release of pro-inflammatory mediators, such as cytokines, intercellular adhesion molecules, and matrix metalloproteinases^[18,21,22].

Neurotoxicity occurs through extravasation of proteins and osmotically active solutes that promoting the development of edema and stimulation of proteinases such as thrombin, fibrinogen, and tissue plasminogen activator. The coagulation cascade is activated in conjunction with lysis of red blood cells, which releases potent neurotoxic substances, such as iron, bilirubin, and hemin^[18,21,22].

TO SET THE SEVERITY AND PROGNOSIS

Prognostication is essential for a correct approach. From a practical point of view, the severity of ICH can be established accurately with clinical examination and neuroimaging^[1-5,37]. Glasgow coma scale (GCS) is the most commonly used tool to assess the level of consciousness. Deficits can be established with NIHSS scale^[1-5,37].

Non-contrasted CT scan is the imaging of choice in the acute phase (Recommendation I, Level A). It confirms the bleeding with excellent sensitivity, determines its location, size, ventricular or subarachnoid extension, degree of distortion or displacement structures and the presence of complications such as hydrocephalus or edema^[2,3,37]. It also helps to establish

Table 2 Secondary insults

Systemic	Intracranial
Arterial Hypotension	Intracranial hypertension
Hypoxia	Cerebral hematoma
Hypercapnia - Hypocapnia	Edema
Hyperthermia	Seizures
Hyperglycemia - Hypoglycemia	Vasospasm
Hyponatremia - Hypernatremia	Hydrocephalus
Anemia	Infections
SIRS	
DIC	

SIRS: Systemic inflammatory response syndrome; DIC: Disseminated intravascular coagulation.

prognosis, monitoring the evolution and the response to different therapeutic modalities.

Recent studies have indicated that CT angiography with contrast can be very useful^[38-40]. Extravasation of contrast within or in adjacent areas of hematoma indicates active bleeding. It has been called "spot sign" and predicts hematoma expansion^[38-40] (Figure 4).

Multiple and varied factors (clinical, biochemical, images) have been described as independent predictors of mortality, however, only GCS score and hematoma volume have shown the most predictive power^[1-5,37].

Unlike other neurocritical entities, there is no universally accepted and validated scale for ICH.

Hemphill, basing on multivariable model of their population, detected five independent factors associated with 30-d mortality, developing a risk stratification scale, which is called ICH score^[41] (Table 1). In this scale, mortality increased as the punctuation increased. No patient with an Score of 0 died, whereas all patients with 5 points died^[41]. This scale has been validated externally^[42,43]. Since the original description of ICH score, several scales have been developed, each with their strengths and weaknesses^[44-46].

It is important to note here that any prediction model lacks validity in centers with nihilism, self-fulfilling prophecies, withdrawal support or DNR politics^[9,10].

INITIAL STABILIZATION, ORGANIC HOMEOSTASIS (PHYSIOLOGICAL NEUROPROTECTION), TO AVOID SECONDARY INSULTS

The main objective should be directed to ensure the ABC (patent airway, adequate breathing, oxygenation, and circulation), achieve clinical stability and then, transfer to imaging study. The neurosurgeon should be actively involved in decision-making^[1-5,37] (Figure 5). It is very important to develop a strategy to prevent, detect and correct secondary insults^[2-5,37,47,48] (Table 2).

This strategy has a significant impact on the outcome^[2,3,7,47,48].

The basis of therapeutic of any neurological injury

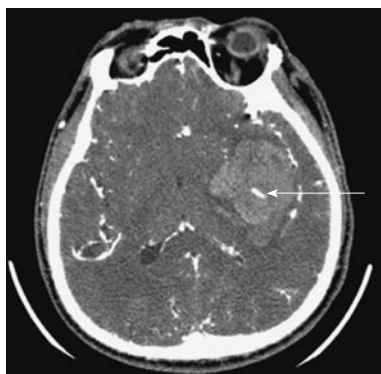


Figure 4 Spot sign.

is to achieve organic homeostasis, which we call "physiological neuroprotection"^[47,48]. From a practical point of view and easy to remember is to maintain healthy 6 principal clinical variables (6 N rule), such as euolemia, paO_2 and paCO_2 levels, temperature, glycemia, and natremia^[47,48]. Target to achieve for each variable are depicted in Figure 6.

To ensure airway patency and oxygenation (ab)

ICH patients are susceptible to develop ventilation and oxygenation alterations^[1-5,37,47-51] due to compromise of defense reflexes of the upper airways such as cough and swallowing, increasing the risk of aspiration of gastric contents^[1-5,47-51]. Pons or supratentorial hemorrhages with mass effect can compromise respiratory rhythm. This population is also at risk for neurogenic or cardiogenic pulmonary edema. We recommend keeping low threshold for intubation and as a general rule all patients in coma should be intubated^[1-5,37,47-51]. Therapeutic targets will be directed to maintain SaO_2 greater than 92% while maintaining normal levels of CO_2 , since hypercapnia causes cerebral vasodilatation and ICP increased, whereas that hypocapnia causes vasoconstriction triggering cerebral ischemia^[1-5,37,47-51].

To optimize circulation (c)

During resuscitation is essential to avoid systemic hypotension, ensuring blood pressure levels that allow adequate cerebral perfusion pressure (CPP)^[1-5,37,47-51]. For this reason, it is necessary to normalize blood volume. The first therapeutic step is infusion of fluids, preferably isotonic saline^[1-5,37,47-51], avoiding hypotonic fluids (0.45% saline, 5% dextrose, Ringer's lactate) that exacerbate brain swelling. Hypertonic saline solutions are an option especially for individuals with signs of herniation, intracranial hypertension or severe hyponatremia. If fluids are not sufficient to ensure adequate blood pressure, vasopressors (noradrenaline) or inotropes (dopamine) should be started^[1-5,37,47-51].

To avoid hyperthermia

Hyperthermia is highly prevalent in neurointensive care^[52]. Initially, elevated temperature is attributable to acute phase response^[52,53], during which inflammatory

mechanisms are triggered, and sympathetic activity is increased^[52,53]. However, directly or indirectly damage of hypothalamus and thermoregulatory centers cannot be excluded^[52,53]. The brain is more warmer than the rest of the body^[52,53]. Hyperthermia exerts its deleterious effects through various mechanisms: it increases levels of excitatory amino acids, cytokines, and reactive oxygen species, inhibits proteolytic enzymes, damages BBB, increases intracranial pressure and triggers apoptotic mechanisms^[53].

Clinical studies have shown a close association between hyperthermia on admission or during the first 24 h and outcome. Moreover, hyperthermia has demonstrated its independent predictive power of poor outcome^[53-55]. Hyperthermia can be controlled with the use of external cooling methods (ice, thermal blankets), internal (intravascular cooling devices) or pharmacological (acetaminophen, aspirin)^[56,57]. Until now, there is no a study that prospectively evaluated the impact of fever control on the outcome nor that is the most suitable method to control fever^[56,57], and due to ethical concerns is very unlikely to be performed ever.

Sodium homeostasis

Disorders of sodium and water metabolism are common in neurocritical ill patients^[58]. Imbalances in the metabolism of sodium produce changes in osmolarity and in water distribution, which in turn, trigger changes in the volume cerebral^[58].

In neurocritical care patients, hyponatremia (serum $\text{Na}^+ < 135 \text{ mEq/L}$) occurs in 15% to 20% of patients, increasing the likelihood of unfavorable outcomes^[58]. The elderly population is very susceptible to this disorder. The causes are varied, highlighting the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt-wasting syndrome (CSWS)^[58,59].

The treatment of hyponatremia, depend on the presence or absence of symptoms and the underlying cause^[58-60]. In the presence of SIADH, fluid restriction is indicated while in the presence of CSWS volume expansion is necessary. In symptomatic cases, hyponatremia should be corrected with hypertonic saline solutions at a slow rate, preferably not more than 10 mmol/liter per day to avoid severe complications such as pontine myelinolysis. Sometimes, fludrocortisone can be used as an adjunct at 0.1-0.4 mg/d^[58-61].

Hypernatremia (serum $\text{Na}^+ > 145 \text{ mEq/L}$) is less frequent^[58]. Its incidence is about 10%, and it is considered a marker of severity of injury with negative predictive power^[58,61]. The most common causes are iatrogenic due to excessive sodium intake or water loss secondary to mannitol infusion^[58,61]. Diabetes insipidus is another disorder to take in mind^[58,61]. The cornerstone of treatment are reposition and retention of water^[58,61]. The replacement should be performed with hypotonic solutions like 5% dextrose or ringer lactate because isotonic saline can exacerbate losses. To avoid loss of water desmopressin at 0.4 mg IV or 100-200 μg *via* nasal route should be utilized. Such doses may

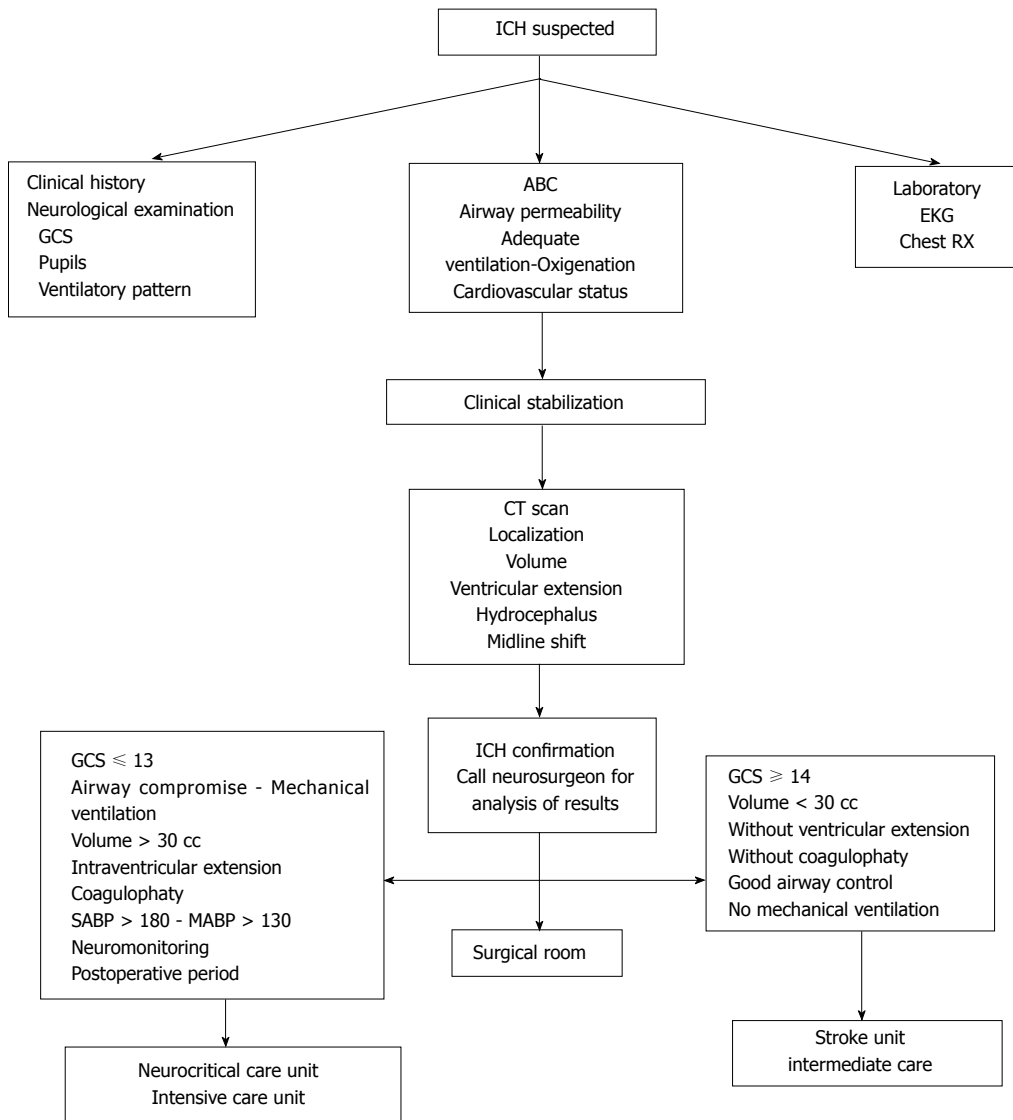


Figure 5 Initial approach of the patients with suspected intracerebral hemorrhage. GCS: Glasgow Coma Scale; ABC: Airway, breathing, circulation; EKG: Electrocardiogram; CT: Computed tomography; ICH: Intracerebral hemorrhage; SABP: Systolic arterial blood pressure; MABP: Mean arterial blood pressure.

be repeated if necessary. Sharp corrections should be avoided^[58,61].

Glycemic control

Blood glucose levels should be kept within a narrow range, avoiding extreme variations since the brain is very vulnerable to such situations^[62,63]. Hypoglycemia should not be allowed in any way and must be corrected immediately^[62,63]. The brain does not tolerate episodes of hypoglycemia as their compensatory mechanisms are exhausted quickly and easily^[62,63].

During injury, the brain increases susceptibility to acute derangements of blood glucose^[62,63]. After injury, the brain increased glucose demand.

Hyperglycemia is common during the acute phase of ICH^[62,64]. Its incidence averages 40% and is independently associated with worse outcome^[61,62,64].

Its etiology is variable, not being clear whether it is a marker of severity or only one component of the metabolic response to injury^[62-64]. Hyperglycemia

contributes to brain damage through various mechanisms that provoke edema and cerebral ischemia^[63]. IV regular insulin is the drug of choice to correct high blood glucose levels but still not yet well determined when starting therapy^[62-65]. Intensive insulin therapy (glucose levels between 80-110 mg/dL) is contraindicated because at these levels starts cellular metabolic distress^[66,67]. The current trend is to maintain the lower limit of about 150 mg/dL and not higher than 200 mg/dL^[2,3,37,62,65].

Gastrointestinal care nutrition

The gastrointestinal tract is of vital importance in patients with brain injury^[68]. Multiple hormones and neuropeptides are released by the brain and intestine in response to injury, establishing an interaction finely regulated by enteric nerve plexus and the autonomic nervous system^[68]. In ICH patients, a number of factors combine to break the normal physiology, including hypothalamic damage, intracranial

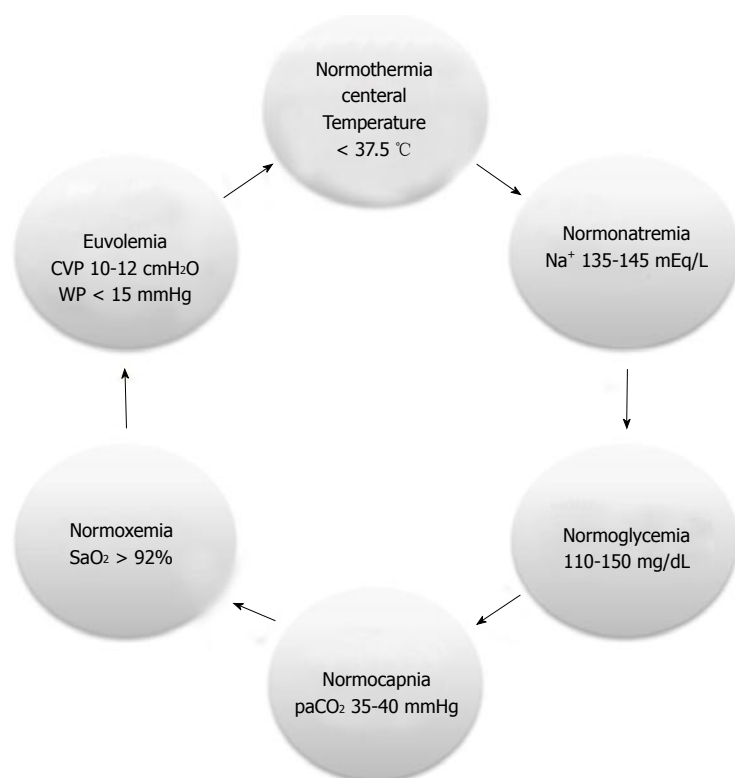


Figure 6 Physiological neuroprotection 6 N rules. CVP: Central venous pressure; WP: Wedge pressure; SaO₂: Oxygen arterial saturation; Na⁺: Serum sodium levels; paCO₂: Carbon dioxide arterial levels.

hypertension, prolonged fasting, mechanical ventilation, drugs (vasopressors, anticonvulsants, opioids, antibiotics, corticosteroids), inflammation (cytokines), hypoalbuminemia, electrolyte imbalances^[68,69]. The most important complications are gastrointestinal bleeding, diarrhea, gastroparesis and ileus, which favor bacterial translocation and malnutrition, sepsis and multiorgan dysfunction^[68,69].

The incidence of clinically significant gastrointestinal bleeding (erosive gastritis or stress ulcer) ranges from 0.6% to 6%^[69]. The main substrate for gastric mucosal damage is the presence of inadequate splanchnic perfusion^[69]. Risk factors are mechanical ventilation (> 48 h), coagulopathy, severe traumatic brain and spinal cord injury^[69]. Some principles are relevant for management, to avoid arterial hypotension and some drugs (steroids, noradrenaline); early nutrition and protection with proton pump inhibitors or local agents^[69]. H₂ receptors blockers are not recommended because they are associated with encephalopathy, interaction with anticonvulsants and modify the local pH favoring bacterial colonization and pneumonia^[69].

Constipation is common after neuroinjury with a negative impact upon outcome^[68]. Incidence rates are between 30% to 60%^[68]. Predisposing factors are immobility, fasting, electrolyte disturbances, and drugs (opioids, sedatives, dopamine). Its prevention is based on adequate fluid and electrolyte balance, rich-fiber diet and laxatives^[68].

Diarrhea is a complication with a prevalence of 8% to 21%^[68]. Fever, hypothermia, hypoalbuminemia, sepsis, multiple organ dysfunction, broad spectrum antibiotics, enteral nutrition, and clostridium difficile (CD) colonization are predisposing factors^[68].

Brain injury, determines a hypermetabolic state, with exaggerated protein catabolism^[68,70]. During injury, the brain increases its metabolic requirements^[62,70]. Nutrition should become one of the key goals of therapy. Malnourished patients are more prone to developing infectious complications, bedsores, gastrointestinal bleeding, all associated with poor outcomes^[68]. Enteral feeding must be supplied early with low calories (25-30 kcal/kg per day), 40% of which in the form of lipids and 15%-20% as protein (1.5-2 g/kg per day) accompanied by a regimen of glycemic control and the contribution of fiber, vitamins, oligoelements and pharmaconutrients (glutamine, arginine)^[70].

SPECIFIC THERAPIES DIRECTED TO ICH

Seizures control

The incidence of seizures after ICH varied between 4.6% and 8.2%^[71]. Acute seizures should be treated following classical algorithms since they are associated with increased cerebral metabolism, ICP and midline shift contributing to secondary injury^[71-76]. Lobar location and small hematomas are independent predictors of early seizures^[72]. Although antiepileptic drugs (AEDs) may reduce the incidence of seizures in cortical and subcortical hemorrhages^[72], their prophylactic use is not recommended because it is unclear their efficacy and impact over final outcome^[73,74]. Phenytoin use was associated with more fever burden and worse outcomes after ICH^[74]. Electroencephalographic seizures without clinical manifestations occur in around 30% of patients after ICH^[75]. Nonconvulsive seizures are associated with early hematoma growth and a trend toward poor outcome^[76]. Continuous EEG monitoring should be

considered in all patients with a decreased level of consciousness without clear reason to justify^[2]. Current Guidelines recommended anti-epileptic treatment for up to one month, after which therapy should be discontinued in the absence of seizures^[2,37].

Hydrocephalus and ventricular extension of bleeding

There are two mechanisms involved in the genesis of acute hydrocephalus: extrinsic compression of ventricular system by proximity (thalamic, cerebellar hematomas); displacing midline structures (putaminal hematomas); or obstruction of CSF circulation by clots^[1,2,4,37,77]. Hydrocephalus causes impairment of consciousness, intracranial hypertension and cerebral ischemia, being an independent predictor of mortality and poor outcome^[77].

The extent of bleeding to the ventricular space complicates about 40% of spontaneous ICHs^[2,4,37,77-80].

Intraventricular blood is a poor prognostic factor^[2,4,37,77-80]. Its volume determines the predictive power, being lethal when exceeding 20 cc, due to hydrocephalus, intracranial hypertension and ischemia of the cerebral cortex^[2,4,37,77-80]. External ventricular drainage is a therapeutic option but insufficient and ineffective when used as a single measure^[2,4,37,77-81].

Patency of the ventriculostomy is difficult to maintain due to frequent plugging clots. Thrombolytic drugs were tested with different protocols and doses^[2,4,37,78-82]. Studies with small numbers of patients showed a trend to reduce need for definitive ventricle peritoneal shunts, and decrease mortality rates with acceptable functional outcomes; however, there is an increased risk of infectious or hemorrhagic complications^[2,4,37,78-82].

CLEAR-IVH study evaluated the strategy of external ventricular drainage more rtPA instillation^[82]. Resolution rates of clots were significantly higher with shorter permanence time of ventriculostomy in rtPA group^[82]. By contrast, symptomatic bleeding rate was higher in the group rtPA. Mortality rates not changed significantly^[82]. The study had several methodological limitations, for example; selection criteria for study inclusion, did not include location of bleeding or extension of intraventricular hemorrhage; management of known factors that influence rates of bleeding such as blood pressure levels or coagulation state not were considerate and the study was not designed to assess long-term functional outcome^[82], a situation that is being evaluated in CLEAR III study^[83].

Endoscopically removal of the clot and controlled lumbar drainage are promising therapeutic alternatives that need large-scale validation^[79-81]. Preliminary results indicate that lumbar drainage after radiological permeation of third and four ventricles was associated with a reduction in the need for permanent ventricular shunting^[78,80].

Intracranial hypertension

Although ICH causes structural changes in brain parenchyma and intracranial hemodynamics than potentially

increase ICP, is unclear its prevalence, temporal profile and the impact that intracranial hypertension have on the outcome.

Intracranial hypertension is more common immediately after bleeding^[84]. Elevated ICP only have an impact on the outcome only in comatose patients^[85]. There was not relationship between ICP values at any time and outcome at 6 mo^[86].

An observational study of ICP recordings in patients with IVH and ICH of less than 30 mL found that the percentage of readings above 30 mmHg was an independent predictor of mortality ($P < 0.001$) and disability at 30 d ($P = 0.01$)^[87]. Kamel and Hemphill analyzed ICH patients with ICP monitoring. Seventy percent of them presented at least one episode of ICP above 20 mmHg while, in 63%, ICP exceeded 25 mmHg. Intracranial hypertension was less frequent in older and infratentorial hemorrhages and was not related to poor outcome^[88].

Recently, a prospective, randomized controlled study assessed the impact of ICP monitoring in the management of supratentorial ICH. The risk of herniation was lower in ICP group (10.9% vs 20.5%, $P = 0.04$). At 6 mo, mortality and disability were lower in ICP group (6.5% vs 9.1%, $P < 0.05$)^[89].

Current recommendations are based on low level of evidence (Class IIb C). However, they suggest ICP monitoring in comatose patients with signs of herniation, hydrocephalus or widespread ventricular hemorrhage^[2,3,37].

Specific treatment of intracranial hypertension

The treatment of intracranial hypertension has been extrapolated from severe head trauma^[2,3,37]. Briefly, after evacuating hemorrhage when were indicated, we follow a staggered, step by step, phased, sequential pathway^[1-4,37,90]. CT scans are performed periodically^[1-4,37,90].

We begin with general measures (sedation, analgesia, prevention and correction of secondary insults) positioning the head in a neutral position at 30 degrees of horizontal^[1-4,37,90]. If ICP remains high, we continue with CSF drainage at not more than 20 mL per hour. If we don't have ventricular drainage or if it resulted ineffective, we start osmotherapy with hypertonic saline or mannitol until the limit of sodium or serum osmolality of 155 mEq/L or 320 mosm/kg respectively^[1-4,37,90]. After this measures, if ICP remains increased, we hyperventilate slightly, maintaining paco_2 levels between 30 and 35 mmHg. At this point, we indicate monitoring of cerebral oxygenation. We do not utilize neuromuscular paralysis unless strictly necessary for ICP normalization. Mean arterial pressure would be titled to a CPP target between 55-70 mmHg^[1-4,37,90].

The non-response to initial therapy, define a state of "refractory intracranial hypertension". Prior to the adoption of "second level" measures (barbiturates at high doses, hypothermia, decompressive craniectomy) we performed indomethacin test^[90].

Optimal levels of arterial blood pressure

Elevated arterial blood pressure (ABP) levels are common in the acute phase of ICH^[2,3,37,91]. Etiology is multifactorial^[2,3,37,91]. There are arguments for and against their control. Those who are in favor of lowering the pressure levels are based on that hypertension is associated with poor outcomes^[92] and may cause expansion of the hematoma^[28,93]. INTERACT study, randomized patients to intensive BP control (target SBP 140 mmHg) vs traditional management (SBP 180 mmHg) within 6 h of ICH onset, showed a trend towards reduction in hematoma growth in the intensive treatment group, without increase the rate of neurological deterioration or other adverse events^[94].

ATACH I study demonstrated safety of nicardipine for acute reduction of BP in acute ICH^[95], while ADAPT trial showed that control arterial hypertension to a target of SBP of lower than 150 mmHg within 24 h of onset did not produce clinically or CBF changes in perihematomal region^[96].

INTERACT II trial^[97], randomized patients with spontaneous ICH and elevated SBP (≥ 150 and ≤ 220 mmHg) to a strategy of intensive control (SBP < 140 mmHg) vs guideline-recommendations (SBP < 180 mmHg) within 6 h of symptoms onset, showed a borderline decrease in poor outcome at 90 d (OR = 0.87, 95%CI: 0.75-1.01; $P = 0.06$)^[97].

ATACH II trial^[98] is an ongoing multi-center, randomized phase III trial to determine the efficacy of early, intensive, BP control initiated within 4.5 h of symptom onset^[98]. The expansion of window from 3 to 4.5 h was based on ATACH-I that suggests a reduction of hematoma expansion, death and disability in patients treated within 4.5 h after symptom onset^[98].

SCORE-IT is an ancillary study of ATACH II that tests the hypothesis that patients with a Spot Sign will receive clinical benefit from intensive ABP reduction^[99].

With regard to pharmacological management, its preferably use agents that do not cause cerebral vasodilation and sudden hypotension, so labetalol (loading dose of 10-20 mg in 1-2 min, repeated every 1-20 min until the desired level of blood pressure were reached or until a maximum dose of 200 mg) or nicardipine (5-15 mg/h) are good options^[2,3,37].

Venous thromboembolism prevention in ICH

Venous thromboembolism (VTE) is one of the most feared complications of ICH. The incidence varies between 2%-17%, with a mortality rate of 5%^[2-4, 37,100,101].

Risk factors for VTE are: older age, female gender, obesity, prolonged bed-rest, legs paralysis, lobar hematoma, great volume, NIHSS score ≥ 12 , withdrawal of antithrombotic treatment, and pro-hemostatic agents such as prothrombin complex or recombinant activated factor VII^[102]. For optimal selection of strategy for VTE prevention is crucial for maintaining the balance between risk of hematoma enlargement and VTE. Strategies to prevent VTE in ICH patients are

pharmacological and nonpharmacological^[103]. Non-pharmacological agents are graduated compression stockings (CS), intermittent pneumatic compression (IPC) plantar venous pump, vena cava filters and early mobilization^[103].

VICTORIA study compared the combination of IPC with CS vs CS alone. The combination of the two strategies was significantly superior in reducing the risk of VTE^[104].

CLOTS II study^[105], showed that CS positioned to the root of the thighs are superior to the CS positioned below the knees. In CLOTS III, IPC was associated with a significant reduction in the risk of VTE^[106].

The main indication for vena cava filters is represented by the absolute contraindication to anticoagulant therapy^[107], so, it is reasonable to reserve filters for patients with very high risk of VTE^[107]. The role of early mobilization for prevention of VTE is controversial and unclear^[108].

Systematic reviews and meta-analysis in terms of efficacy and safety of pharmacological prophylaxis for prevention of VTE balanced with the risk of hematoma expansion showed that unfractionated heparin or low molecular weight heparins significantly reduces the risk of pulmonary embolism, whereas not reduced the risk of DVT or death from all causes^[109,110]. No increase in the risk of hematoma expansion was observed^[110]. Based on actual recommendations^[2,3,37,110] a possible flow chart for VTE prevention in ICH is depicted in Figure 7.

URGENT REVERSAL THERAPY IN ANTITHROMBOTIC, ANTICOAGULANTS-RELATED INTRACEREBRAL HEMORRHAGE

The urgent reversal therapy represents the cornerstone of management of antithrombotic-related ICH. It aims is to restore adequate hemostasis by neutralizing the anticoagulant or antiplatelet activity with specific antidotes, avoiding hematoma growth and devastating consequences of drugs induced coagulopathy^[102].

Specific antidotes are available only for few anti-coagulants, such as vitamin K antagonists (VKAs), unfractionated heparin (UFH) and idrabiotaparinux, not marketed yet.

Protamine sulfate is the recognized specific antidote for unfractionated heparin^[111]. The goal of protamine for the reversal of unfractionated heparin is the normalization of activated partial thromboplastin time (aPTT). Protamine has a partial effect on LMWH reversal. Therefore higher dose may be necessary^[112].

Despite intravenous administration of vitamin K1 (VK1) represents the most used for VKAs reverse (recommendation IA), it is not the only strategy because it's slow onset of action and because need between 12-16 h to complete its action^[111-113]. VK1 should be always administered together with prothrombin complex

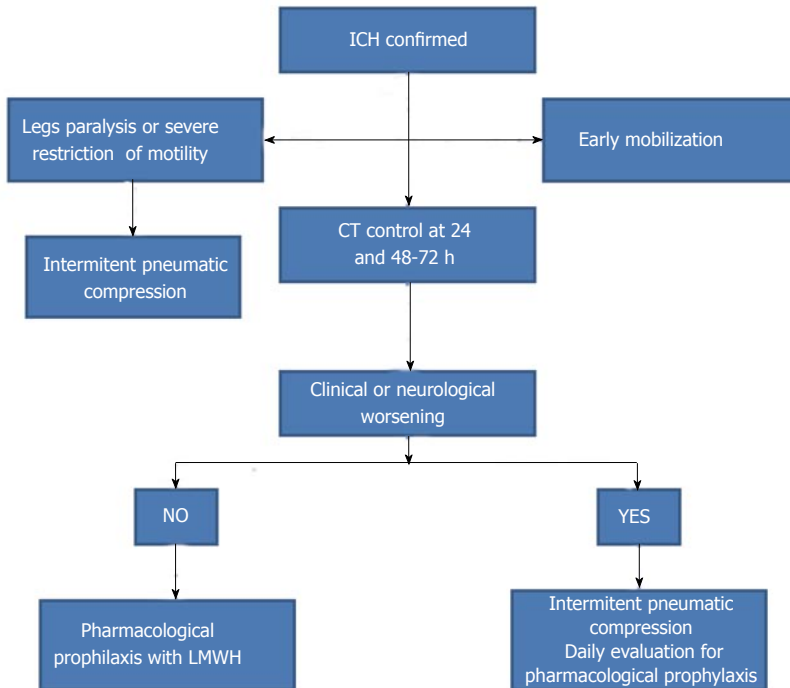


Figure 7 Algorithm suggested for venous thromboembolism prevention in intracerebral hemorrhage. ICH: Intracerebral hemorrhage; CT: Computed tomography; LMWH: Low molecular weight heparin.

concentrates (PCCs), rFVII or fresh frozen plasma (FFP) because all these agents prove VK dependent coagulation factors^[102].

PCCs, rFVII and FFP have short half time, therefore, the missed dose of VK1 could determine the rebound of International Normalized Ratio (INR) values after their pharmacological action^[102-111].

The goal of urgent VKAs reversal in ICH is to bring the INR values ≤ 1.4 within 2-4 h^[102,114-116]. At the end of pro-hemostatic infusion, INR should be re-checked, and the adjunctive dose should be infused if its values continue to be ≥ 1.5 ^[102,116] (Figure 8).

PCCs a derivate of plasma contain three or four non-activated vitamin K depending coagulation factors (II, VII, IX, and X). Three factors PCCs lack for Factor VII^[117]. PPCs restore INR and reduce hematoma enlargement rates, but it is controversial if it's associated with mortality reduction or better functional outcome^[117,118].

PCCs are considered the first choice for VKAs urgent reversal from many scientific Societies^[2,37]. Limitation of PCCs derived from thromboembolic risk. Thromboembolic burden of PCCs is lower than 2%^[119].

FFP is another effective strategy that leads to VKAs neutralization in 4-6 h but has it certain limitations, such as volume overload, especially in elderly or patients with limited cardiac reserve; delays in time due to thawing and blood group typing; infectious risk and TRALI (transfusion acute lung injury)^[102].

Many reports have demonstrated that rFVII is effective for prompt VKAs reversal in few minutes without volume overload, but its use in this context is not recommended due to high risk of arterial and venous thromboembolic complications^[119,120].

Recent trials have demonstrated that new oral anticoagulants, dabigatran, apixaban, edoxaban, rivaroxaban, reduce the risk of ICH in comparison with warfarin, however this effect is not negligible, ranging from 0.2% to 0.4% per year. Case-fatality rate of new oral anticoagulants related ICH is not significantly different compared with warfarin ranged between 50%-70%^[121-123].

After urgent reversal, coagulation parameters should be performed but, again, it is unclear if adjunctive dose should be administered if coagulation parameters remain abnormal^[102]. Therefore the proposed coagulation assays, such as aPTT, aPTT ratio, dTT, PT, PT ratio and anti-Xa, are suboptimal tools for predicting the response to pro-hemostatic agents, whereas methods aimed at global evaluation of hemostasis, such as thromboelastogram, platelet reactivity, and thrombin generation might be more useful^[102,124].

Which is the optimal strategy for urgent reversal of antiplatelet activity in antiplatelet-related ICH remain unclear? Despite platelets transfusion or intravenous desmopressin have been proposed, literature failed to demonstrate their beneficial effect in ICH^[125,126]. Desmopressin has been proposed as a nonspecific strategy in antiplatelet related bleeding. However, its role in antiplatelet-related ICH is uncertain^[127].

SURGERY OR NOT SURGERY: HAMLET'S DILEMMA

Despite the time elapsed the debate continues, with an open end. The removal of the hematoma reduces

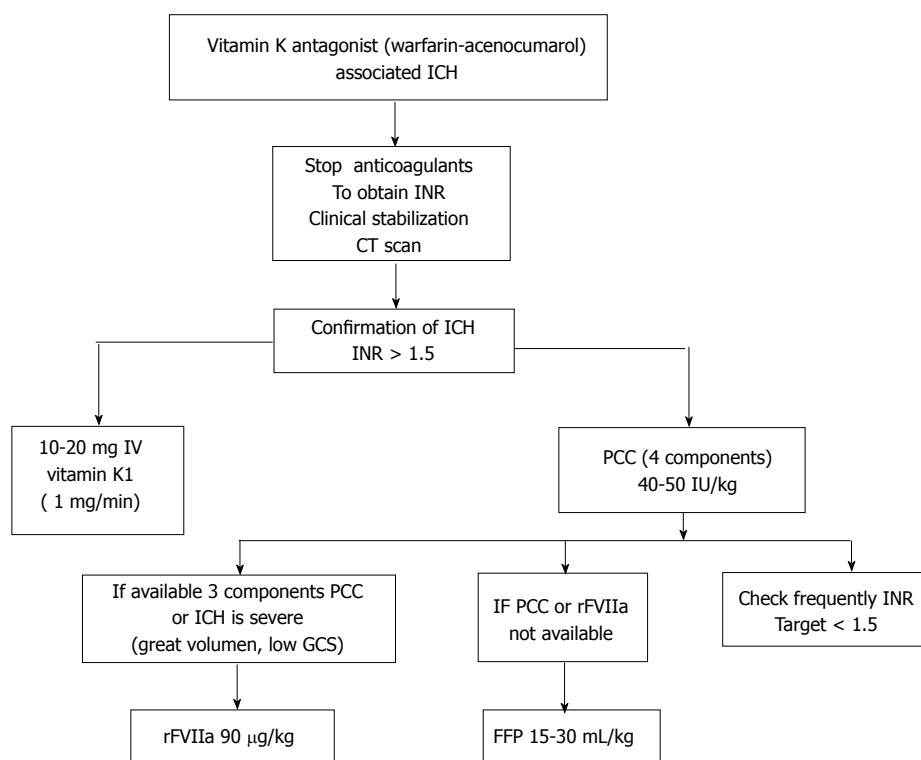


Figure 8 Algorithm to urgent reversal therapy in vitamin K antagonist related intracerebral hemorrhage. ICH: Intracerebral hemorrhage; INR: International normalization ratio; CT: Computed tomography; IV: Intravenous; PCC: Prothrombin concentrate complex; IU: International units; GCS: Glasgow coma scale; rFVIIa: Activated recombinant seven-factor; FFP: Fresh frozen plasma.

its volume, corrects distortions and displacements, reduces ICP and improves CPP. Furthermore, abort the continuation of neurotoxic and inflammatory cascades^[2,4,37,128-131]. However, these theoretical advantages must be weighed against parenchyma damage required to access to the hematoma^[128-131].

Most neurosurgeons agree to operate lobar or cerebellar hematomas in patients who deteriorate clinically, however, uncertainty remains regarding deep hemorrhages^[128-131].

Current guidelines, recommend surgical treatment in the following situations^[2,3,37]: (1) cerebellar hematomas of more than 3 cm in diameter in patients who deteriorate clinically with secondary hydrocephalus or compression of brainstem or fourth ventricle (grade C); (2) hemorrhages secondary to arteriovenous malformations, angiomas, cavernous malformations, aneurysms, *etc.* (grade C); and (3) lobar hematomas of moderate or larger volume in young patients with neurological impairment (grade B).

The STICH study, enrolled patients with supratentorial hemorrhages within the initial 72 h of symptoms onset, and then randomized them to medical vs surgical treatment based on the principle of uncertainty about the usefulness of surgery^[129]. Mortality and functional outcomes were the same for both groups^[129]. A small subgroup of patients was identified as able to evolve better. They are individuals aware (GCS between 9 and 12 points) with superficial hematomas, located at 1 cm or less in the cerebral cortex^[129].

The STICH II study^[130], compare surgery (within 12 h of randomization), with conservative medical treatment in patients with spontaneous supratentorial hemorrhage, lobar, superficial (≤ 1 cm from the cortex), with a volume between 10 and 100 mL, without ventricular extension of bleeding within 48 h of onset of symptoms^[130]. There were no differences between groups in terms of mortality or disability rates at 6 mo. The subgroup of patients with worse initial prognosis evidenced a favorable trend if they were operated early^[130].

A recent meta-analysis found that surgery seemed effective in patients with a higher consciousness level (GCS score 9-12) operated within eight hours of symptom onset^[131].

Recently, the European Stroke Organization declares that there is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH, but early surgery may be of value for patients with a GCS score 9-12^[37].

There is a worldwide tendency to operate these patients with minimally invasive techniques, either by endoscopy or stereotactic with or without the combination of a catheter into the hematoma to instill fibrinolytic in order to accelerate the resolution of hematoma^[2-5,37,131-133].

MISTIE II study randomized patients to a control group or clot aspiration with rtPA in putaminal (58%) or lobar (42%) hemorrhages above 25 mL and GCS < 14 and NIHSS > 6. Higher rates of clot removal and lower mortality were observed in the treated group^[132].

MISTIE II and other trials of minimally invasive surgery (MIS) have shown encouraging results, so a phase III trial started in 2013^[133].

Zhou's meta-analysis concluded that patients who would most benefit from minimally invasive surgery are those between 30 and 80 years with superficial supratentorial hematomas, with volumes between 25 and 40 mL, admitted within 72 h in a good level of consciousness (GCS \geq 9)^[132].

CONCLUSION

The spontaneous ICH is a neurological-neurosurgical emergency far from diminishing its prevalence will increase in the coming years. Despite being one of the most devastating forms of stroke, a light on the horizon looms as a result of advances in knowledge and the results of recent trials. It is extremely important and essential to remove nihilism and self-fulfilling prophecies. A multidisciplinary approach is essential. Set the prognosis helps us in the process of decision-making and communication with the patient or their relatives. The therapy should be individualized and follows a deep pathophysiologic analysis. The cornerstones of therapy are correct evaluation, avoiding secondary insults through neuroprotection physiological measures, intensive control of blood pressure especially in acute and rapid reversal of antithrombotic and anticoagulant drugs. The role of surgery is still open to debate especially in deep bleeding.

REFERENCES

- 1 Qureshi AI, Tuhir S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001; **344**: 1450-1460 [PMID: 11346811 DOI: 10.1056/NEJM200105103441907]
- 2 Morgenstern LB, Hemphill JC, Anderson C, Becker K, Broderick JP, Connolly ES, Greenberg SM, Huang JN, MacDonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; **41**: 2108-2129 [PMID: 20651276 DOI: 10.1161/STR.0b013e3181ec611b]
- 3 Rodríguez-Yáñez M, Castellanos M, Freijo MM, López Fernández JC, Martí-Fàbregas J, Nombela F, Simal P, Castillo J, Díez-Tejedor E, Fuentes B, Alonso de Leciñana M, Alvarez-Sabin J, Arenillas J, Calleja S, Casado I, Dávalos A, Díaz-Otero F, Egido JA, Gállego J, García Pastor A, Gil-Núñez A, Gilo F, Irimia P, Lago A, Maestre J, Masjuan J, Martínez-Sánchez P, Martínez-Vila E, Molina C, Morales A, Purroy F, Ribó M, Roquer J, Rubio F, Segura T, Serena J, Tejada J, Vivancos J. Clinical practice guidelines in intracerebral haemorrhage. *Neurologia* 2013; **28**: 236-249 [PMID: 21570742 DOI: 10.1016/j.nrl.2011.03.010]
- 4 Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet* 2009; **373**: 1632-1644 [PMID: 19427958 DOI: 10.1016/S0140-6736(09)60371-8]
- 5 Staykov D, Huttner HB, Köhrmann M, Bardutzky J, Schellinger PD. Novel approaches to the treatment of intracerebral haemorrhage. *Int J Stroke* 2010; **5**: 457-465 [PMID: 21050402 DOI: 10.1111/j.1747-4949.2010.00487.x]
- 6 Nietzsche F. Obras completas de Nietzsche. Aguilar: Buenos Aires, 1963
- 7 Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, Longstreth WT. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology* 2001; **56**: 766-772 [PMID: 11274312 DOI: 10.1212/WNL.56.6.766]
- 8 Merton RK. Teoría y estructura sociales. México: FCE, 1980
- 9 Hemphill JC, Newman J, Zhao S, Johnston SC. Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. *Stroke* 2004; **35**: 1130-1134 [PMID: 15044768 DOI: 10.1161/01.STR.0000125858.71051.ca]
- 10 Zahuranec DB, Morgenstern LB, Sánchez BN, Resnicow K, White DB, Hemphill JC. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology* 2010; **75**: 626-633 [PMID: 20610832 DOI: 10.1212/WNL.0b013e3181ed9cc9]
- 11 Diringner MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med* 2001; **29**: 635-640 [PMID: 11373434 DOI: 10.1097/00003246-200103000-00031]
- 12 Terént A, Asplund K, Farahmand B, Henriksson KM, Norrving B, Stegmayr B, Wester PO, Asberg KH, Asberg S. Stroke unit care revisited: who benefits the most? A cohort study of 105,043 patients in Riks-Stroke, the Swedish Stroke Register. *J Neurol Neurosurg Psychiatry* 2009; **80**: 881-887 [PMID: 19332423 DOI: 10.1136/jnnp.2008.169102]
- 13 Kurtz P, Fitts V, Sumer Z, Jalon H, Cooke J, Kvetan V, Mayer SA. How does care differ for neurological patients admitted to a neurocritical care unit versus a general ICU? *Neurocrit Care* 2011; **15**: 477-480 [PMID: 21519958 DOI: 10.1007/s12028-011-9539-2]
- 14 Zurasky JA, Aiyagari V, Zazulia AR, Shackelford A, Diringner MN. Early mortality following spontaneous intracerebral hemorrhage. *Neurology* 2005; **64**: 725-727 [PMID: 15728302 DOI: 10.1212/01.WNL.0000152045.56837.58]
- 15 Fan JS, Huang HH, Chen YC, Yen DH, Kao WF, Huang MS, Huang CI, Lee CH. Emergency department neurologic deterioration in patients with spontaneous intracerebral hemorrhage: incidence, predictors, and prognostic significance. *Acad Emerg Med* 2012; **19**: 133-138 [PMID: 22320363 DOI: 10.1111/j.1553-2712.2011.01285.x]
- 16 Naidech AM, Bernstein RA, Bassin SL, Garg RK, Liebling S, Bendok BR, Batjer HH, Bleck TP. How patients die after intracerebral hemorrhage. *Neurocrit Care* 2009; **11**: 45-49 [PMID: 19199079 DOI: 10.1007/s12028-009-9186-z]
- 17 Moon JS, Janjua N, Ahmed S, Kirmani JF, Harris-Lane P, Jacob M, Ezzeddine MA, Qureshi AI. Prehospital neurologic deterioration in patients with intracerebral hemorrhage. *Crit Care Med* 2008; **36**: 172-175 [PMID: 18007267 DOI: 10.1097/01.CCM.0000297876.62464.6B]
- 18 Rincon F, Mayer SA. Novel therapies for intracerebral hemorrhage. *Curr Opin Crit Care* 2004; **10**: 94-100 [PMID: 15075717 DOI: 10.1097/00075198-200404000-00003]
- 19 Sutherland GR, Auer RN. Primary intracerebral hemorrhage. *J Clin Neurosci* 2006; **13**: 511-517 [PMID: 16769513 DOI: 10.1016/j.jocn.2004.12.012]
- 20 Vernooij MW, Heeringa J, de Jong GJ, van der Lugt A, Breteler MM. Cerebral microbleed preceding symptomatic intracerebral hemorrhage in a stroke-free person. *Neurology* 2009; **72**: 763-765 [PMID: 19237708 DOI: 10.1212/01.wnl.0000343047.74665.89]
- 21 Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; **5**: 53-63 [PMID: 16361023 DOI: 10.1016/S1474-4422(05)70283-0]
- 22 Wang J, Doré S. Inflammation after intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2007; **27**: 894-908 [PMID: 17033693 DOI: 10.1038/sj.jcbfm.9600403]
- 23 Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, Spilker J, Tomsick TA, Duldner J, Broderick JP. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 2002; **33**: 2631-2635 [PMID: 12411653 DOI: 10.1161/01.STR.0000035284.12699.84]
- 24 Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke* 2003; **34**: 224-229 [PMID: 12511778 DOI: 10.1161/01.STR.0000046458.67968.E4]
- 25 Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral

- hemorrhage. *Neurology* 2004; **63**: 1059-1064 [PMID: 15452298 DOI: 10.1212/01.WNL.0000138428.40673.83]
- 26 **Steiner T**, Bösel J. Options to restrict hematoma expansion after spontaneous intracerebral hemorrhage. *Stroke* 2010; **41**: 402-409 [PMID: 20044536 DOI: 10.1161/STROKEAHA.109.552919]
- 27 **Kazui S**, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke* 1997; **28**: 2370-2375 [PMID: 9412616 DOI: 10.1161/01.STR.28.12.2370]
- 28 **Ohwaki K**, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 2004; **35**: 1364-1367 [PMID: 15118169 DOI: 10.1161/01.STR.0000128795.38283.4b]
- 29 **Qureshi AI**, Hanel RA, Kirmani JF, Yahia AM, Hopkins LN. Cerebral blood flow changes associated with intracerebral hemorrhage. *Neurosurg Clin N Am* 2002; **13**: 355-370 [PMID: 12486925 DOI: 10.1016/S1042-3680(02)00012-8]
- 30 **Nath FP**, Kelly PT, Jenkins A, Mendelow AD, Graham DI, Teasdale GM. Effects of experimental intracerebral hemorrhage on blood flow, capillary permeability, and histochemistry. *J Neurosurg* 1987; **66**: 555-562 [PMID: 3559721 DOI: 10.3171/jns.1987.66.4.0555]
- 31 **Bullock R**, Brock-Utne J, van Dellen J, Blake G. Intracerebral hemorrhage in a primate model: effect on regional cerebral blood flow. *Surg Neurol* 1988; **29**: 101-107 [PMID: 3336844 DOI: 10.1016/0090-3019(88)90065-1]
- 32 **Qureshi AI**, Wilson DA, Hanley DF, Traystman RJ. No evidence for an ischemic penumbra in massive experimental intracerebral hemorrhage. *Neurology* 1999; **52**: 266-272 [PMID: 9932942 DOI: 10.1212/WNL.52.2.266]
- 33 **Zazulia AR**, Diringer MN, Videen TO, Adams RE, Yundt K, Aiyagari V, Grubb RL, Powers WJ. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2001; **21**: 804-810 [PMID: 11435792 DOI: 10.1097/00004647-200107000-00005]
- 34 **Herweh C**, Jüttler E, Schellinger PD, Klotz E, Jenetzky E, Orakcioglu B, Sartor K, Schramm P. Evidence against a perihemorrhagic penumbra provided by perfusion computed tomography. *Stroke* 2007; **38**: 2941-2947 [PMID: 17901391 DOI: 10.1161/STROKEAHA.107.486977]
- 35 **Kim-Han JS**, Kopp SJ, Dugan LL, Diringer MN. Perihematomal mitochondrial dysfunction after intracerebral hemorrhage. *Stroke* 2006; **37**: 2457-2462 [PMID: 16960094 DOI: 10.1161/01.STR.0000240674.99945.4e]
- 36 **Vespa PM**. Metabolic penumbra in intracerebral hemorrhage. *Stroke* 2009; **40**: 1547-1548 [PMID: 19286575 DOI: 10.1161/STROKEAHA.108.542803]
- 37 **Steiner T**, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJ, Krieger D, Mendelow AD, Molina C, Montaner J, Overgaard K, Petersson J, Roine RO, Schmutzhard E, Schwerdtfeger K, Stapf C, Tatlisumak T, Thomas BM, Toni D, Unterberg A, Wagner M. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014; **9**: 840-855 [PMID: 25156220 DOI: 10.1111/ijss.12309]
- 38 **Huynh TJ**, Demchuk AM, Dowlatshahi D, Gladstone DJ, Krisehek O, Kiss A, Hill MD, Molina CA, Rodriguez-Luna D, Dzialowski I, Silva Y, Czlonkowska A, Lum C, Boulanger JM, Gubitz G, Bhatia R, Padma V, Roy J, Kase CS, Aviv RI. Spot sign number is the most important spot sign characteristic for predicting hematoma expansion using first-pass computed tomography angiography: analysis from the PREDICT study. *Stroke* 2013; **44**: 972-977 [PMID: 23444309 DOI: 10.1161/STROKEAHA.111.000410]
- 39 **Romero JM**, Brouwers HB, Lu J, Delgado Almandoz JE, Kelly H, Heit J, Goldstein J, Rosand J, Gonzalez RG. Prospective validation of the computed tomographic angiography spot sign score for intracerebral hemorrhage. *Stroke* 2013; **44**: 3097-3102 [PMID: 24021687 DOI: 10.1161/STROKEAHA.113.002752]
- 40 **Brouwers HB**, Goldstein JN, Romero JM, Rosand J. Clinical applications of the computed tomography angiography spot sign in acute intracerebral hemorrhage: a review. *Stroke* 2012; **43**: 3427-3432 [PMID: 23132779 DOI: 10.1161/STROKEAHA.112.664003]
- 41 **Hemphill JC**, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001; **32**: 891-897 [PMID: 11283388 DOI: 10.1161/01.STR.32.4.891]
- 42 **Godoy DA**, Boccio A. ICH score in a rural village in the Republic of Argentina. *Stroke* 2003; **34**: e150-e151; author reply e150-e151 [PMID: 12947164 DOI: 10.1161/01.STR.0000089493.23505.CA]
- 43 **Clarke JL**, Johnston SC, Farrant M, Bernstein R, Tong D, Hemphill JC. External validation of the ICH score. *Neurocrit Care* 2004; **1**: 53-60 [PMID: 16174898]
- 44 **Godoy DA**, Piñero G, Di Napoli M. Predicting mortality in spontaneous intracerebral hemorrhage: can modification to original score improve the prediction? *Stroke* 2006; **37**: 1038-1044 [PMID: 16514104 DOI: 10.1161/01.STR.0000206441.79646.49]
- 45 **Hwang BY**, Appelboom G, Kellner CP, Carpenter AM, Kellner MA, Gigante PR, Sander Connolly E. Clinical grading scales in intracerebral hemorrhage. *Neurocrit Care* 2010; **13**: 141-151 [PMID: 20490715 DOI: 10.1007/s12028-010-9382-x]
- 46 **Bruce SS**, Appelboom G, Piazza M, Hwang BY, Kellner C, Carpenter AM, Bagiella E, Mayer S, Connolly ES. A comparative evaluation of existing grading scales in intracerebral hemorrhage. *Neurocrit Care* 2011; **15**: 498-505 [PMID: 21394545 DOI: 10.1007/s12028-011-9518-7]
- 47 **Diez-Tejedor E**, Fuentes B. Homeostasis as basis of acute stroke treatment: stroke units are the key. *Cerebrovasc Dis* 2005; **20** Suppl 2: 129-134 [PMID: 16327263 DOI: 10.1159/000089366]
- 48 **Auer RN**. Non-pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia. *Ann N Y Acad Sci* 2001; **939**: 271-282 [PMID: 11462780 DOI: 10.1111/j.1749-6632.2001.tb03635.x]
- 49 **Goldstein JN**, Gilson AJ. Critical care management of acute intracerebral hemorrhage. *Curr Treat Options Neurol* 2011; **13**: 204-216 [PMID: 21222062 DOI: 10.1007/s11940-010-0109-2]
- 50 **Rincon F**, Mayer SA. Clinical review: Critical care management of spontaneous intracerebral hemorrhage. *Crit Care* 2008; **12**: 237 [PMID: 19108704 DOI: 10.1186/cc7092]
- 51 **Gujjar AR**, Deibert E, Manno EM, Duff S, Diringer MN. Mechanical ventilation for ischemic stroke and intracerebral hemorrhage: indications, timing, and outcome. *Neurology* 1998; **51**: 447-451 [PMID: 9710017 DOI: 10.1212/WNL.51.2.447]
- 52 **Kilpatrick MM**, Lowry DW, Firlik AD, Yonas H, Marion DW. Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery* 2000; **47**: 850-855; discussion 855-856 [PMID: 11014424 DOI: 10.1097/00006123-200010000-00011]
- 53 **Badjatia N**. Hyperthermia and fever control in brain injury. *Crit Care Med* 2009; **37**: S250-S257 [PMID: 19535955 DOI: 10.1097/CCM.0b013e3181aa5e8d]
- 54 **Schwarz S**, Häfner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology* 2000; **54**: 354-361 [PMID: 10668696 DOI: 10.1212/WNL.54.2.354]
- 55 **Rincon F**, Lyden P, Mayer SA. Relationship between temperature, hematoma growth, and functional outcome after intracerebral hemorrhage. *Neurocrit Care* 2013; **18**: 45-53 [PMID: 23001769 DOI: 10.1007/s12028-012-9779-9]
- 56 **Badjatia N**. Fever control in the neuro-ICU: why, who, and when? *Curr Opin Crit Care* 2009; **15**: 79-82 [PMID: 19578318 DOI: 10.1097/MCC.0b013e32832922e9]
- 57 **Lord AS**, Karinja S, Lantigua H, Carpenter A, Schmidt JM, Claassen J, Agarwal S, Connolly ES, Mayer SA, Badjatia N. Therapeutic temperature modulation for fever after intracerebral hemorrhage. *Neurocrit Care* 2014; **21**: 200-206 [PMID: 24420694 DOI: 10.1007/s12028-013-9948-5]
- 58 **Tisdall M**, Crocker M, Watkiss J, Smith M. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. *J Neurosurg Anesthesiol* 2006; **18**: 57-63 [PMID: 16369141 DOI: 10.1097/01.ana.0000191280.05170.0f]
- 59 **Harrigan MR**. Cerebral salt wasting syndrome: a review. *Neurosurgery* 1996; **38**: 152-160 [PMID: 8747964 DOI: 10.1097/0

- 0006123-199601000-00035]
- 60 **Overgaard-Steensen C.** Initial approach to the hyponatremic patient. *Acta Anaesthesiol Scand* 2011; **55**: 139-148 [PMID: 21029052 DOI: 10.1111/j.1399-6576.2010.02311.x]
- 61 **Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K.** The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care* 2008; **12**: R162 [PMID: 19094227 DOI: 10.1186/cc7162]
- 62 **Godoy DA, Di Napoli M, Rabinstein AA.** Treating hyperglycemia in neurocritical patients: benefits and perils. *Neurocrit Care* 2010; **13**: 425-438 [PMID: 20652767 DOI: 10.1007/s12028-010-9404-8]
- 63 **Garg R, Chaudhuri A, Munschauer F, Dandona P.** Hyperglycemia, insulin, and acute ischemic stroke: a mechanistic justification for a trial of insulin infusion therapy. *Stroke* 2006; **37**: 267-273 [PMID: 16306459 DOI: 10.1161/01.STR.0000195175.29487.30]
- 64 **Godoy DA, Piñero GR, Svampa S, Papa F, Di Napoli M.** Hyperglycemia and short-term outcome in patients with spontaneous intracerebral hemorrhage. *Neurocrit Care* 2008; **9**: 217-229 [PMID: 18300001 DOI: 10.1007/s12028-008-9063-1]
- 65 **Godoy DA, Di Napoli M, Biestro A, Lenhardt R.** Perioperative glucose control in neurosurgical patients. *Anesthesiol Res Pract* 2012; **2012**: 690362 [PMID: 22400022 DOI: 10.1155/2012/690362]
- 66 **Vespa P, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, Glenn T, Martin N, Hovda D.** Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Crit Care Med* 2006; **34**: 850-856 [PMID: 16505665 DOI: 10.1097/01.CCM.0000201875.12245.6F]
- 67 **Oddo M, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapovich ND, Levine JM, Le Roux P, Mayer SA.** Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. *Crit Care Med* 2008; **36**: 3233-3238 [PMID: 18936695 DOI: 10.1097/CCM.0b013e31818f4026]
- 68 **Btaiche IF, Chan LN, Pleva M, Kraft MD.** Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. *Nutr Clin Pract* 2010; **25**: 32-49 [PMID: 20130156 DOI: 10.1177/0884533609357565]
- 69 **Schirmer CM, Kornbluth J, Heilman CB, Bhardwaj A.** Gastrointestinal prophylaxis in neurocritical care. *Neurocrit Care* 2012; **16**: 184-193 [PMID: 21748505 DOI: 10.1007/s12028-011-9580-1]
- 70 **Krenitsky J.** Glucose control in the intensive care unit: a nutrition support perspective. *Nutr Clin Pract* 2011; **26**: 31-43 [PMID: 21266695 DOI: 10.1177/0884533610392237]
- 71 **Yang TM, Lin WC, Chang WN, Ho JT, Wang HC, Tsai NW, Shih YT, Lu CH.** Predictors and outcome of seizures after spontaneous intracerebral hemorrhage. Clinical article. *J Neurosurg* 2009; **111**: 87-93 [PMID: 19301969 DOI: 10.3171/2009.2.JNS081622]
- 72 **Passero S, Rocchi R, Rossi S, Ulivelli M, Vatti G.** Seizures after spontaneous supratentorial intracerebral hemorrhage. *Epilepsia* 2002; **43**: 1175-1180 [PMID: 12366733 DOI: 10.1046/j.1528-1157.2002.00302.x]
- 73 **Messé SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE.** Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care* 2009; **11**: 38-44 [PMID: 19319701 DOI: 10.1007/s12028-009-9207-y]
- 74 **Naidech AM, Garg RK, Liebling S, Levasseur K, Macken MP, Schuele SU, Batjer HH.** Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke* 2009; **40**: 3810-3815 [PMID: 19797183 DOI: 10.1161/STROKEAHA.109.559948]
- 75 **Claassen J, Jetté N, Chum F, Green R, Schmidt M, Choi H, Jirsch J, Frontera JA, Connolly ES, Emerson RG, Mayer SA, Hirsch LJ.** Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology* 2007; **69**: 1356-1365 [PMID: 17893296 DOI: 10.1212/01.wnl.0000281664.02615.6c]
- 76 **Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, Saver J, Nuwer MR, Frazee JG, McArthur DA, Martin NA.** Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology* 2003; **60**: 1441-1446 [PMID: 12743228 DOI: 10.1212/01.WNL.0000063316.47591.B4]
- 77 **Phan TG, Koh M, Vierkant RA, Wijndicks EF.** Hydrocephalus is a determinant of early mortality in putaminal hemorrhage. *Stroke* 2000; **31**: 2157-2162 [PMID: 10978045 DOI: 10.1161/01.STR.31.9.2157]
- 78 **Staykov D, Huttner HB, Struffert T, Ganslandt O, Doerfler A, Schwab S, Bardutzky J.** Intraventricular fibrinolysis and lumbar drainage for ventricular hemorrhage. *Stroke* 2009; **40**: 3275-3280 [PMID: 19679848 DOI: 10.1161/STROKEAHA.109.551945]
- 79 **Hinson HE, Hanley DF, Ziai WC.** Management of intraventricular hemorrhage. *Curr Neurol Neurosci Rep* 2010; **10**: 73-82 [PMID: 20425231 DOI: 10.1007/s11910-010-0086-6]
- 80 **Gaberel T, Magheru C, Emery E.** Management of non-traumatic intraventricular hemorrhage. *Neurosurg Rev* 2012; **35**: 485-494; discussion 494-495 [PMID: 22732889 DOI: 10.1007/s10143-012-0399-9]
- 81 **Dey M, Jaffe J, Stadnik A, Awad IA.** External ventricular drainage for intraventricular hemorrhage. *Curr Neurol Neurosci Rep* 2012; **12**: 24-33 [PMID: 22002766 DOI: 10.1007/s11910-011-0231-x]
- 82 **Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, Coplin W, Narayan R, Haines S, Cruz-Flores S, Zuccarello M, Brock D, Awad I, Ziai WC, Marmarou A, Rhoney D, McBee N, Lane K, Hanley DF.** Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke* 2011; **42**: 3009-3016 [PMID: 21868730 DOI: 10.1161/STROKEAHA.110.610949]
- 83 **Ziai WC, Tuhim S, Lane K, McBee N, Lees K, Dawson J, Butcher K, Vespa P, Wright DW, Keyl PM, Mendelow AD, Kase C, Wijman C, Lapointe M, John S, Thompson R, Thompson C, Mayo S, Reilly P, Janis S, Awad I, Hanley DF.** A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *Int J Stroke* 2014; **9**: 536-542 [PMID: 24033910 DOI: 10.1111/ijls.12097]
- 84 **Janny P, Papo I, Chazal J, Colnet G, Barretto LC.** Intracranial hypertension and prognosis of spontaneous intracerebral haematomas. A correlative study of 60 patients. *Acta Neurochir (Wien)* 1982; **61**: 181-186 [PMID: 7072549 DOI: 10.1007/BF01740083]
- 85 **Ropper AH, King RB.** Intracranial pressure monitoring in comatose patients with cerebral hemorrhage. *Arch Neurol* 1984; **41**: 725-728 [PMID: 6743063 DOI: 10.1001/archneur.1984.04050180047016]
- 86 **Fernandes HM, Siddique S, Banister K, Chambers I, Wooldridge T, Gregson B, Mendelow AD.** Continuous monitoring of ICP and CPP following ICH and its relationship to clinical, radiological and surgical parameters. *Acta Neurochir Suppl* 2000; **76**: 463-466 [PMID: 11450068 DOI: 10.1007/978-3-7091-6346-7_96]
- 87 **Ziai WC, Melnychuk E, Thompson CB, Awad I, Lane K, Hanley DF.** Occurrence and impact of intracranial pressure elevation during treatment of severe intraventricular hemorrhage. *Crit Care Med* 2012; **40**: 1601-1608 [PMID: 22430237 DOI: 10.1097/CCM.0b013e318241e380]
- 88 **Kamel H, Hemphill JC.** Characteristics and sequelae of intracranial hypertension after intracerebral hemorrhage. *Neurocrit Care* 2012; **17**: 172-176 [PMID: 22833445 DOI: 10.1007/s12028-012-9744-7]
- 89 **Zeng J, Zheng P, Tong W, Fang W.** Decreased risk of secondary brain herniation with intracranial pressure monitoring in patients with haemorrhagic stroke. *BMC Anesthesiol* 2014; **14**: 19 [PMID: 24650002 DOI: 10.1186/1471-2253-14-19]
- 90 **Godoy DA, Rabinstein AA, Biestro A, Ainslie PN, Di Napoli M.** Effects of indomethacin test on intracranial pressure and cerebral hemodynamics in patients with refractory intracranial hypertension: a feasibility study. *Neurosurgery* 2012; **71**: 245-257; discussion 257-258 [PMID: 22531711 DOI: 10.1227/NEU.0b013e318256b9f5]
- 91 **Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, Divani AA, Reddi AS.** Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med* 2007; **25**: 32-38 [PMID: 17157679 DOI: 10.1016/j.ajem.2006.07.008]
- 92 **Zhang Y, Reilly KH, Tong W, Xu T, Chen J, Bazzano LA, Qiao D, Ju Z, Chen CS, He J.** Blood pressure and clinical outcome

- among patients with acute stroke in Inner Mongolia, China. *J Hypertens* 2008; **26**: 1446-1452 [PMID: 18551022 DOI: 10.1097/HJH.0b013e328300a24a]
- 93 **Rodriguez-Luna D**, Piñeiro S, Rubiera M, Ribo M, Coscojuela P, Pagola J, Flores A, Muchada M, Ibarra B, Meler P, Sanjuan E, Hernandez-Guillamon M, Alvarez-Sabin J, Montaner J, Molina CA. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. *Eur J Neurol* 2013; **20**: 1277-1283 [PMID: 23647568 DOI: 10.1111/ene.12180]
 - 94 **Anderson CS**, Huang Y, Wang JG, Arima H, Neal B, Peng B, Heeley E, Skulina C, Parsons MW, Kim JS, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Heritier S, Morgenstern LB, Chalmers J. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008; **7**: 391-399 [PMID: 18396107 DOI: 10.1016/S1474-4422(08)70069-3]
 - 95 **Qureshi AI**. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH): rationale and design. *Neurocrit Care* 2007; **6**: 56-66 [PMID: 17356194]
 - 96 **Butcher KS**, Jeerakathil T, Hill M, Demchuk AM, Dowlatshahi D, Coutts SB, Gould B, McCourt R, Asdaghi N, Findlay JM, Emery D, Shuaib A. The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial. *Stroke* 2013; **44**: 620-626 [PMID: 23391776 DOI: 10.1161/STROKEAHA.111.000188]
 - 97 **Anderson CS**, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; **368**: 2355-2365 [PMID: 23713578 DOI: 10.1056/NEJMoa1214609]
 - 98 **Qureshi A**, Palesch Y. Expansion of recruitment time window in antihypertensive treatment of acute cerebral hemorrhage (ATACH) II trial. *J Vasc Interv Neurol* 2012; **5**: 6-9 [PMID: 23230458]
 - 99 **Goldstein J**, Brouwers H, Romero J, McNamara K, Schwab K, Greenberg S, Rosand J. SCORE-IT: the Spot Sign score in restricting ICH growth-an Atach-II ancillary study. *J Vasc Interv Neurol* 2012; **5**: 20-25 [PMID: 23230461]
 - 100 **Kappelle LJ**. Preventing deep vein thrombosis after stroke: strategies and recommendations. *Curr Treat Options Neurol* 2011; **13**: 629-635 [PMID: 21909622 DOI: 10.1007/s11940-011-0147-4]
 - 101 **André C**, de Freitas GR, Fukujima MM. Prevention of deep venous thrombosis and pulmonary embolism following stroke: a systematic review of published articles. *Eur J Neurol* 2007; **14**: 21-32 [PMID: 17222109 DOI: 10.1111/j.1468-1331.2006.01536.x]
 - 102 **Masotti L**, Di Napoli M, Godoy DA, Rafanelli D, Liunbruno G, Koumpourous N, Landini G, Pampana A, Cappelli R, Poli D, Prisco D. The practical management of intracerebral hemorrhage associated with oral anticoagulant therapy. *Int J Stroke* 2011; **6**: 228-240 [PMID: 21557810 DOI: 10.1111/j.1747-4949.2011.00595.x]
 - 103 **Caprini JA**. Mechanical methods for thrombosis prophylaxis. *Clin Appl Thromb Hemost* 2010; **16**: 668-673 [PMID: 19850588 DOI: 10.1177/1076029609348645]
 - 104 **Lacut K**, Bressollette L, Le Gal G, Etienne E, De Tintinac A, Renault A, Rouhart F, Besson G, Garcia JF, Mottier D, Oger E. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. *Neurology* 2005; **65**: 865-869 [PMID: 16186525 DOI: 10.1212/01.wnl.0000176073.80532.a2]
 - 105 **Dennis M**, Sandercock PA, Reid J, Graham C, Murray G, Venables G, Rudd A, Bowler G. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet* 2009; **373**: 1958-1965 [PMID: 19477503 DOI: 10.1016/S0140-6736(09)60941-7]
 - 106 **CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration**. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med* 2010; **153**: 553-562 [PMID: 20855784 DOI: 10.7326/0003-4819-153-9-20101020-00280]
 - 107 **Imberti D**, Ageno W, Dentali F, Donadini M, Manfredini R, Gallerani M. Retrievable vena cava filters: a clinical review. *J Thromb Thrombolysis* 2012; **33**: 258-266 [PMID: 22240968 DOI: 10.1007/s11239-011-0671-9]
 - 108 **Langhorne P**, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. *Cerebrovasc Dis* 2010; **29**: 352-360 [PMID: 20130401 DOI: 10.1159/000278931]
 - 109 **Dentali F**, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007; **146**: 278-288 [PMID: 17310052 DOI: 10.7326/0003-4819-146-4-200702200-00007]
 - 110 **Masotti L**, Godoy DA, Napoli MD, Rabinstein AA, Paciaroni M, Ageno W. Pharmacological prophylaxis of venous thromboembolism during acute phase of spontaneous intracerebral hemorrhage: what do we know about risks and benefits? *Clin Appl Thromb Hemost* 2012; **18**: 393-402 [PMID: 22609819 DOI: 10.1177/1076029612441055]
 - 111 **Ageno W**, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e44S-e88S [PMID: 22315269 DOI: 10.1378/chest.11-2292]
 - 112 **van Veen JJ**, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, Makris M. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis* 2011; **22**: 565-570 [PMID: 21959588 DOI: 10.1097/MBC.0b013e3283494b3c]
 - 113 **Ageno W**, Garcia D, Aguilar MI, Douketis J, Finazzi G, Imberti D, Iorio A, Key NS, Lim W, Marietta M, Prisco D, Sarode R, Testa S, Tosetto A, Crowther M. Prevention and treatment of bleeding complications in patients receiving vitamin K antagonists, part 2: Treatment. *Am J Hematol* 2009; **84**: 584-588 [PMID: 19610020 DOI: 10.1002/ajh.21469]
 - 114 **Hanger HC**, Geddes JA, Wilkinson TJ, Lee M, Baker AE. Warfarin-related intracerebral haemorrhage: better outcomes when reversal includes prothrombin complex concentrates. *Intern Med J* 2013; **43**: 308-316 [PMID: 23176226 DOI: 10.1111/imj.12034]
 - 115 **Levi M**, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost* 2011; **9**: 1705-1712 [PMID: 21729240 DOI: 10.1111/j.1538-7836.2011.04432.x]
 - 116 **Witt DM**, Delate T, Hylek EM, Clark NP, Crowther MA, Dentali F, Ageno W, Martinez KD, Garcia DA. Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes. *Thromb Res* 2013; **132**: 770-775 [PMID: 24521790 DOI: 10.1016/j.thromres.2013.10.024]
 - 117 **Kuwashiro T**, Yasaka M, Itabashi R, Nakagaki H, Miyashita F, Naritomi H, Minematsu K. Effect of prothrombin complex concentrate on hematoma enlargement and clinical outcome in patients with anticoagulant-associated intracerebral hemorrhage. *Cerebrovasc Dis* 2011; **31**: 170-176 [PMID: 21135553 DOI: 10.1159/000321766]
 - 118 **Dowlatshahi D**, Butcher KS, Asdaghi N, Nahrianiak S, Bernbaum ML, Giulivi A, Wasserman JK, Poon MC, Coutts SB. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. *Stroke* 2012; **43**: 1812-1817 [PMID: 22556194 DOI: 10.1161/STROKEAHA.112.652065]
 - 119 **Dentali F**, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost* 2011; **106**: 429-438 [PMID: 21800002 DOI: 10.1160/TH11-01-0052]
 - 120 **Ingerslev J**, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation. *J Postgrad Med* 2007; **53**: 17-22 [PMID: 17244965 DOI: 10.4103/0022-3859.30322]
 - 121 **Lauer A**, Pfeilschifter W, Schaffer CB, Lo EH, Foerch C. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies. *Lancet Neurol* 2013; **12**: 394-405 [PMID: 23518332 DOI: 10.1016/S1474-4422(13)70049-8]
 - 122 **Majeed A**, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S. Management and outcomes of major bleeding during treatment with

- dabigatran or warfarin. *Circulation* 2013; **128**: 2325-2332 [PMID: 24081972 DOI: 10.1161/CIRCULATIONAHA.113.002332]
- 123 **Piccini JP**, Garg J, Patel MR, Lokhnygina Y, Goodman SG, Becker RC, Berkowitz SD, Breithardt G, Hacke W, Halperin JL, Hankey GJ, Nessel CC, Mahaffey KW, Singer DE, Califf RM, Fox KA. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. *Eur Heart J* 2014; **35**: 1873-1880 [PMID: 24658769 DOI: 10.1093/eurheartj/ehu083]
 - 124 **Hoffman M**, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. *J Thromb Haemost* 2012; **10**: 1478-1485 [PMID: 22632160 DOI: 10.1111/j.1538-7836.2012.04793.x]
 - 125 **Creutzfeldt CJ**, Weinstein JR, Longstreth WT, Becker KJ, McPharlin TO, Tirschwell DL. Prior antiplatelet therapy, platelet infusion therapy, and outcome after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2009; **18**: 221-228 [PMID: 19426894 DOI: 10.1016/j.jstrokecerebrovasdis.2008.10.007]
 - 126 **de Gans K**, de Haan RJ, Majoie CB, Koopman MM, Brand A, Dijkgraaf MG, Vermeulen M, Roos YB. PATCH: platelet transfusion in cerebral haemorrhage: study protocol for a multicentre, randomised, controlled trial. *BMC Neurol* 2010; **10**: 19 [PMID: 20298539 DOI: 10.1186/1471-2377-10-19]
 - 127 **Naidech AM**, Maas MB, Levasseur-Franklin KE, Liotta EM, Guth JC, Berman M, Rosenow JM, Lindholm PF, Bendok BR, Prabhakaran S, Bernstein RA, Kwaan HC. Desmopressin improves platelet activity in acute intracerebral hemorrhage. *Stroke* 2014; **45**: 2451-2453 [PMID: 25005444 DOI: 10.1161/STROKEAHA.114.006061]
 - 128 **Kreitzer N**, Adeoye O. An update on surgical and medical management strategies for intracerebral hemorrhage. *Semin Neurol* 2013; **33**: 462-467 [PMID: 24504609 DOI: 10.1055/s-0033-1364210]
 - 129 **Mendelow AD**, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MD, Barer DH. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* 2005; **365**: 387-397 [PMID: 15680453 DOI: 10.1016/S0140-6736(05)17826-X]
 - 130 **Mendelow AD**, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet* 2013; **382**: 397-408 [PMID: 23726393 DOI: 10.1016/S0140-6736(13)60986-1]
 - 131 **Gregson BA**, Broderick JP, Auer LM, Batjer H, Chen XC, Juvela S, Morgenstern LB, Pantazis GC, Teernstra OP, Wang WZ, Zuccarello M, Mendelow AD. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke* 2012; **43**: 1496-1504 [PMID: 22511006 DOI: 10.1161/STROKEAHA.111.640284]
 - 132 **Zhou X**, Chen J, Li Q, Ren G, Yao G, Liu M, Dong Q, Guo J, Li L, Guo J, Xie P. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke* 2012; **43**: 2923-2930 [PMID: 22989500 DOI: 10.1161/STROKEAHA.112.667535]
 - 133 **Barnes B**, Hanley DF, Carhuapoma JR. Minimally invasive surgery for intracerebral haemorrhage. *Curr Opin Crit Care* 2014; **20**: 148-152 [PMID: 24553341 DOI: 10.1097/MCC.0000000000000077]

P- Reviewer: Cattermole G, Lin J, Llompart-Pou J, Nayci A

S- Editor: Tian YL **L- Editor:** A **E- Editor:** Wu HL



Myeloproliferative and thrombotic burden and treatment outcome of thrombocythemia and polycythemia patients

Jan Jacques Michiels

Jan Jacques Michiels, International Collaborations and Research on Myeloproliferative Neoplasms (ICAR.MPN) and Goodheart Institute and Foundation in Nature Medicine and Health, 3069 AT Rotterdam, The Netherlands

Author contributions: Michiels JJ solely contributed to this paper.

Conflict-of-interest statement: The author declares no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Jan Jacques Michiels, MD, PhD, Multi-disciplinary Internist, International Collaborations and Research on Myeloproliferative Neoplasms (ICAR.MPN) and Goodheart Institute and Foundation in Nature Medicine and Health, Erasmus Tower, Veenmos 13, 3069 AT Rotterdam, The Netherlands. goodheartcenter@upcmail.nl
Telephone: +31-62-6970534

Received: March 3, 2015

Peer-review started: March 4, 2015

First decision: April 10, 2015

Revised: June 10, 2015

Accepted: July 11, 2015

Article in press: July 14, 2015

Published online: August 4, 2015

platelet-mediated thrombosis in early, intermediate and advanced stages of thrombocythemia in MPN-T. If left untreated both microvascular and major thrombosis frequently do occur in MPN-T, but can easily be cured and prevented by low dose aspirin as platelet counts are above $350 \times 10^9/L$. The thrombotic risk stratification in the retrospective Bergamo study has been performed in 100 essential thrombocythemia (ET) patients not treated with aspirin thereby overlooking the discovery in 1985 of aspirin responsive platelet-mediated arteriolar and arterial thrombotic tendency in MPN-T disease of ET and polycythemia vera (PV) patients. The Bergamo definition of high thrombotic risk and its persistence in the 2012 International Prognostic Score for ET is based on statistic mystification and not applicable for low and intermediate MPN-T disease burden in ET and PV patients on aspirin. With the advent of molecular screening of MPN patients, MPN-T disease associated with significant leukocytosis, thrombocytosis, constitutional symptoms and/or moderate splenomegaly are candidates for low dose pegylated interferon (Pegasis^R, 45 $\mu g/mL$ once per week or every two weeks) as the first line myeloreductive treatment option in JAK2^{V617F} mutated MPN-T disease in ET and PV patients. If non-responsive to or side effects induced by IFN, hydroxyurea is the second line myelosuppressive treatment option in JAK2^{V617F} mutated ET and PV patients with increased MPN-T disease burden.

Key words: Myeloproliferative neoplasms; Essential thrombocythemia; Polycythemia vera; JAK2^{V617F} mutation; Aspirin; Interferon; Hydroxyurea

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Abstract

Prospective studies indicate that the risk of microvascular and major thrombosis in untreated thrombocythemia in various myeloproliferative neoplasms (MPN-T) is not age dependent and causally related to

Core tip: Spontaneous endogenous erythroid colony formation and low serum erythropoietin (EPO) levels are highly specific for JAK2^{V617F} mutated essential thrombocythemia (ET), prodromal polycythemia vera (PV), masked PV and classical PV. The quantitation

of JAK2^{V617F} mutation allele burden plays a key-role in the diagnostic work-up and staging of ET, PV and MF patients. The JAK2^{V617F} mutation allele burden in heterozygous mutated ET is low but high in combined heterozygous - homozygous or homozygous mutated PV. The combined use of JAK2^{V617F} mutation load, spleen size and pretreatment bone marrow biopsy are of major prognostic significance and therapeutic importance in ET and PV patients. Large Prospective Unmet Need studies are warranted to delineate the natural history and outcome of targeted treatment in MPN patients of various molecular etiology during long-term or life long follow-up.

Michiels JJ. Myeloproliferative and thrombotic burden and treatment outcome of thrombocythemia and polycythemia patients. *World J Crit Care Med* 2015; 4(3): 230-239 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/230.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.230>

INTRODUCTION CLINICAL

MANIFESTATIONS IN PV AND ET

The bleeding manifestations in 100 case histories of hemorrhagic thrombocythemia (HT) ranged from gastrointestinal chronic occult blood loss, melena and hematemesis to mucocutaneous bruises, hematomas, ecchymoses, gum bleedings and secondary bleeding^[1,2]. HT was usually associated with significant leukocytosis and splenomegaly and the platelet count at time of bleeding in 100 HT cases ranged from 800 to above $4000 \times 10^9/L$ (Figure 1, left). The manifestation in erythromelalgic thrombotic thrombocythemia (ETT) in 67 ET and 32 PV patients included erythromelalgia, acrocyanosis, digital gangrene, amaurosis fugax, transient ischemic attacks, stroke, angina pectoris and myocardial infarction, superficial thrombophlebitis and deep vein thrombosis^[3]. The platelet count at time of ETT in ET and PV patients ranged from 400 to $2000 \times 10^9/L$ in ET patients and from 350 to $1250 \times 10^9/L$ in PV patients (Figure 1, left).

Microvascular ischemic and thrombotic complications such as erythromelalgia, atypical and typical TIAs, ocular transient ischemic events and migraine-like headache dominate the clinical picture at presentation ET and early PV. In contrast to the inefficacy of coumadin, control of platelet function with low dose aspirin and reduction of platelet counts to normal prevented the recurrence of microvascular circulation disturbances in the end-arterial microvasculature of the cerebral, coronary and peripheral circulation^[3-10]. Clinicians should be aware that a starting low dose of aspirin, 50 mg daily, in symptomatic ET patients complicated by erythromelalgia induces a slow relief of pain and gradual inhibition of platelet cyclo-oxygenase (COX-1), as it takes 4 to 6 d to completely inhibit platelet COX-1

and to relief erythromelalgia by such a low dose of aspirin. Consequently, symptomatic thrombocythemia vera patients at time of presentation with microvascular circulation disturbances or major thrombosis should be immediately treated with a loading dose of aspirin 300 to 500 mg followed by a low maintenance dose of 50 to 80 mg daily. Our observational studies on a high frequency of microvascular thrombotic complications in particular indicate the existence of platelet thrombophilia in thrombocythemia for which aspirin is a safe and effective antithrombotic agent in ET and PV patients (A1 level of evidence). Low dose aspirin at platelet counts in excess of $1250 \pm 250 \times 10^9/L$ is frequently associated with the paradoxical occurrence of thrombosis and bleeding (ETT + HT, Figure 1). Bleedings spontaneously occur at platelet count in excess of $1250 \pm 250 \times 10^9/L$ due to an acquired von Willebrand Disease (AVWD, type 2A with absence of high and intermediate von Willebrand factor (VWF) multimers increasing in severity at increasing platelet counts to high levels above $1500 \times 10^9/L$ (Figure 1, upper part)^[8]. Correction of the platelet counts to normal (less than $350 \times 10^9/L$) is associated with no recurrences of microvascular events after discontinuation of aspirin^[2,6,7] together with complete correction of the VWF-multimeric pattern and of all VWF-parameters to normal values^[8].

RISK ON MICROVASCULAR AND MAJOR THROMBOSIS IN PV AND ET

The risk stratification for thrombosis by Cortelazzo *et al*^[11] in 1990 in 100 ET patients not treated with aspirin overlooked the 1985 key reference of Michiels *et al*^[3] on the demonstration of aspirin responsive platelet-mediated arteriolar and arterial thrombotic tendency in ET and PV patients. The characteristics of the thrombotic events in the retrospective Bergamo cohort of 100 patients were in Tables 1 and 2.

The age distribution of this cohort of ET did not reflect real life experience since the number of young ET patients was artificially manipulated to one third in the young age group to reach statistical significance. The risk for thrombotic complication was low (1.7%) in MPN-T at young age below 40 years, but was high at age of > 60 years (15%), and moderately increased (6.3%) in the age group of 40 to 60 years not on aspirin^[11]. In the Dutch prospective ET and PV studies the risk of thrombosis in untreated ET and PV is not age dependent and causally related to platelet-mediated thrombosis in the various stages of ET and PV patients^[1-10]. The type and number of 25 arterial and 3 venous thrombotic episodes in 20 out of 100 untreated ET patients in the 1990 Bergamo study were mainly microcirculatory events including digital ischemia, transient ischemic attacks, superficial thrombophlebitis, unusual site of DVT, no stroke, and major thrombosis only in 4, myocardial infarction in 3 and femoral DVT in 1 (Table 2)^[11]. If left untreated symptomatic ET patients with microcirculatory

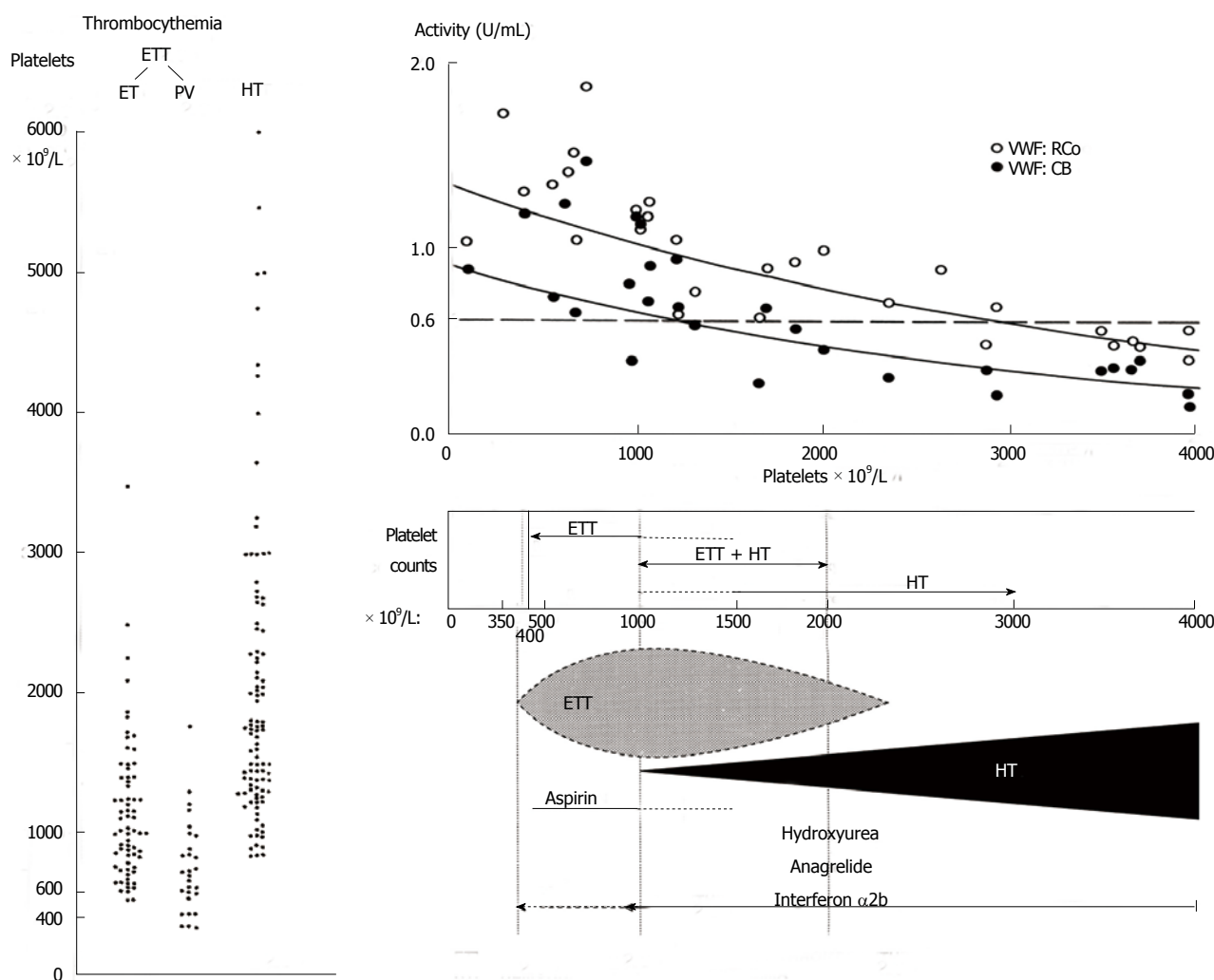


Figure 1 Platelet counts in 100 case histories of hemorrhagic thrombocythemia and 99 cases of erythromelalgic thrombotic thrombocythemia subdivided in patients with essential thrombocythemia and polycythemia vera (left)^[1,2]. The relationship between platelet-mediated microvascular thrombosis in ETT at platelet counts between 350 to 1000 × 10⁹/L in ETT and mucocutaneous bleedings at platelet counts between about 1000 to above 2000 × 10⁹/L in HT patients (Table 3)^[1,7]. The relationship of increasing platelet counts and decreasing von Willebrand factor (VWF) levels, VWF:ristocetane cofactor activity (VWF:RCo), and VWF collagen binding activity (VWF:CB) as the cause of an acquired Von Willebrand Disease (AVWD) type 2A due to proteolysis of large VWF multimers in patients with paradoxical occurrence of ETT and HT and in patients with HT^[6]. HT: Hemorrhagic thrombocythemia; ETT: Erythromelalgic thrombotic thrombocythemia; ET: Essential thrombocythemia; PV: Polycythemia vera.

disturbances are at very high risk for digital ischemia, TIAs, stroke or acute coronary ischemic syndromes. Based on the results of our prospective studies in Table 3^[4,5] we concluded that the stratification in low, intermediate and high thrombotic risk in the 1990 Bergamo study^[11] can only be applied to ET patients not on aspirin. This means that the stratification in aspirin responsive low, intermediate and high thrombotic risk in the retrospective Bergamo ET study is based on statistic misinterpretation and mystification leading to authoritative overtreatment recommendation with hydroxyurea for ET and PV patients on low dose aspirin. The so-called high thrombotic risk ET as defined by a history or presentation of thrombosis at time of diagnosis or by reaching the age 60 years is not in line with the observed low thrombotic incidence in aspirin treated ET and PV patients^[10,12-14]. The 1995 Bergamo prospective randomized clinical trial (RCT)

of 114 ET patients comparing hydroxyurea vs placebo in high thrombotic risk ET patients is unbalanced since 69% of the placebo group and 70% of the HU-treated ET patients did not receive aspirin^[15]. Two of 56 high thrombotic risk ET patients on hydroxyurea had major thrombotic events (one stroke, one myocardial infarction) and 14 of 58 high thrombotic risk ET patients in the placebo group had microcirculatory disturbances in 12, and major thrombosis in 2. However, 10 of these 14 symptomatic patients in the placebo arm manifested aspirin responsive microvascular disturbances but were not on treatment with aspirin^[15]. The conclusion from this RCT is that HU vs low dose aspirin alone in high thrombotic risk ET patients is predicted to be equally effective for the prevention of microvascular circulation disturbances in ET (Figure 1, Table 3)^[4,5]. Consequently, the high thrombotic risk in the 2012 IPSET (International Prognostic Score for ET)^[14] with the indication of

Table 1 Incidence of thrombotic events related to age in 100 patients with essential thrombocythemia not on aspirin in the 1990 Bergamo study^[11]

Age (yr)	No. of patients	Patient/years	Events number	Events % pt/yr
< 40	34	118	2	1.70%
40-60	37	112	7	6.30%
> 60	29	73	11	15%
Total thrombotic events in 20 of 100 ET patients				

ET: Essential thrombocythemia.

Table 2 The type and number of microvascular thrombotic events in the 1990 Bergamo study are very characteristic for untreated thrombocythemia^[11]

Cortelazzo <i>et al</i> ^[11] 1990	No. of patients	No. of events
Total	20	32
Arterial	17	25
Digital ischemia		7
Transient ischemic attacks		15
Stroke		0
Myocardial infarction		3
Venous	3	7
Superficial Thrombophlebitis		3
Femoral DVT		1
Unusual localization DVT		3
Bleeding complications	4	

DVT: Deep vein thrombosis.

hydroxyurea (HU) simple leads to significant HU over-treatment in ET and PV patients on aspirin with a low or intermediate MPN-T disease burden^[12,13].

With the advent of molecular screening of MPN-T patients, it should be realized that WHO-ET patients with less than 50% JAK2^{V617F} mutation load are usually heterozygous, and WHO-PV patients with less than 50% JAK2^{V617F} mutation load are frequently combined heterozygous homozygous positive for the JAK2^{V617F} mutation^[16-18]. In the study of Vannucchi *et al*^[19], the JAK2^{V617F} allele burden in 173 PV ranged from 1%-25% in 33%, from 25%-50% in 29%, from 50% to 75% in 20% and from 75% to 100% in 18%. Treatment consisted of phlebotomy in 49% and cytoreductive therapy (mainly hydroxyurea) in 51%. The JAK2^{V617F} allele mutation burden correlated with MPN disease activity in terms of stimulated erythropoiesis by higher hematocrit and erythrocytes, lower MCV, serum EPO and ferritine, and stimulated myelopoiesis by higher leukocytes, serum LDH and LAP score^[19]. Comparing PV patients with low (1% to 50%) vs high (50%-100%) JAK2^{V617F} allele burden, the relative risks for MPN disease burden increased from 1 to 4 for pruritis, from 1 to 4 for palpable splenomegaly and from 1 to 4 for spleen sizes above 15 cm length diameter on scan. In a subsequent elegant study Vannucchi *et al*^[20] assessed the incidence of thrombosis related to the JAK2 allele burden in a large retrospective study of 962 MPN-T patients subdivided

Table 3 Incidence of thrombotic and bleeding complications in the prospective 1975-1996 Rotterdam study of 68 ET patients during a median follow-up of 6.7 years according to treatment strategy (Van Genderen *et al*^[4,5] 1997)

Treatment strategy	Duration of follow-up person (yr)	Thrombotic events		Bleeding events	
		Events (n)	Events/100 person (yr)	Events (n)	Events/100 person (yr)
Asymptomatic 14 patients					
Watchful waiting	127	27 ¹	33.3	2	1.6
Symptomatic 54 patients					
Low-dose aspirin	139	5	3.6	10 ³	7.2
Platelet reduction	113	10 ²	8.9	2	1.8
Low-dose aspirin + platelet reduction	40	0	-	4	10
Total	419	42		18	

¹Mean platelet count 610, range 410-831 × 10⁹/L at time of thrombotic event; ²Platelet count 624 ± 255 × 10⁹/L at time of thrombotic event; ³Platelet count 1737, range 661-3460 × 10⁹/L at time of bleeding event. These observations by Van Genderen *et al*^[4,5] confirm the concept in Figure 1 on the relationship between platelet-mediated microvascular thrombosis in thrombocythemia at platelet counts between 350 to 1000 × 10⁹/L in ETT and mucocutaneous bleedings at platelet counts of 1000 to above 2000 × 10⁹/L in HT patients.

in 323 PV and 639 ET patients^[20]. Aspirin responsive platelet thrombophilia or microvascular symptoms due to microvessel disorder including migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances were excluded by definition and not considered in this retrospective analysis^[20]. Only major thrombotic events ischemic stroke, transient ischemic attacks, myocardial infarction, angina pectoris, deep vein thrombosis abdominal vein thrombosis, and pulmonary embolism were assessed. The incidence of major thrombotic events in 188 JAK2^{V617F} homozygous MPN patients (JAK2^{V617F} mutation above 50% in 104 PV and 14 ET) and in 587 heterozygous (JAK2^{V617F} mutation less than 50% in 219 PV and 257 ET) and 257 wild type ET patients was assessed and calculated in Table 4 and Figure 2. Anno 2014, JAK2 wild ET are predicted to carry one of the CALR positive in 80%^[21]. Homozygous JAK2^{V617F} positive patients with JAK2^{V617F} mutation above 50% in ET and PV are truly homozygous. Homozygous JAK2^{V617F} mutated MPN patients with a mutation allele load above 50% were older, had higher leukocyte counts, hematocrits and larger spleen volumes indicating advanced MPN disease. One hundred seventy-six patients (18.3%) had a major thrombotic event at diagnosis with a similar frequency in PV (19.2%) and ET (17.8%)^[20]. A similar incidence was found in our analysis of the literature in 1241 ET patients not on aspirin from 14 retrospective studies^[22]. In the Italian study, major thrombosis (usually not on aspirin) occurred in 122 patients (12.7%), corresponding to 14.9% in PV and 11.6% in ET patients and hemorrhages

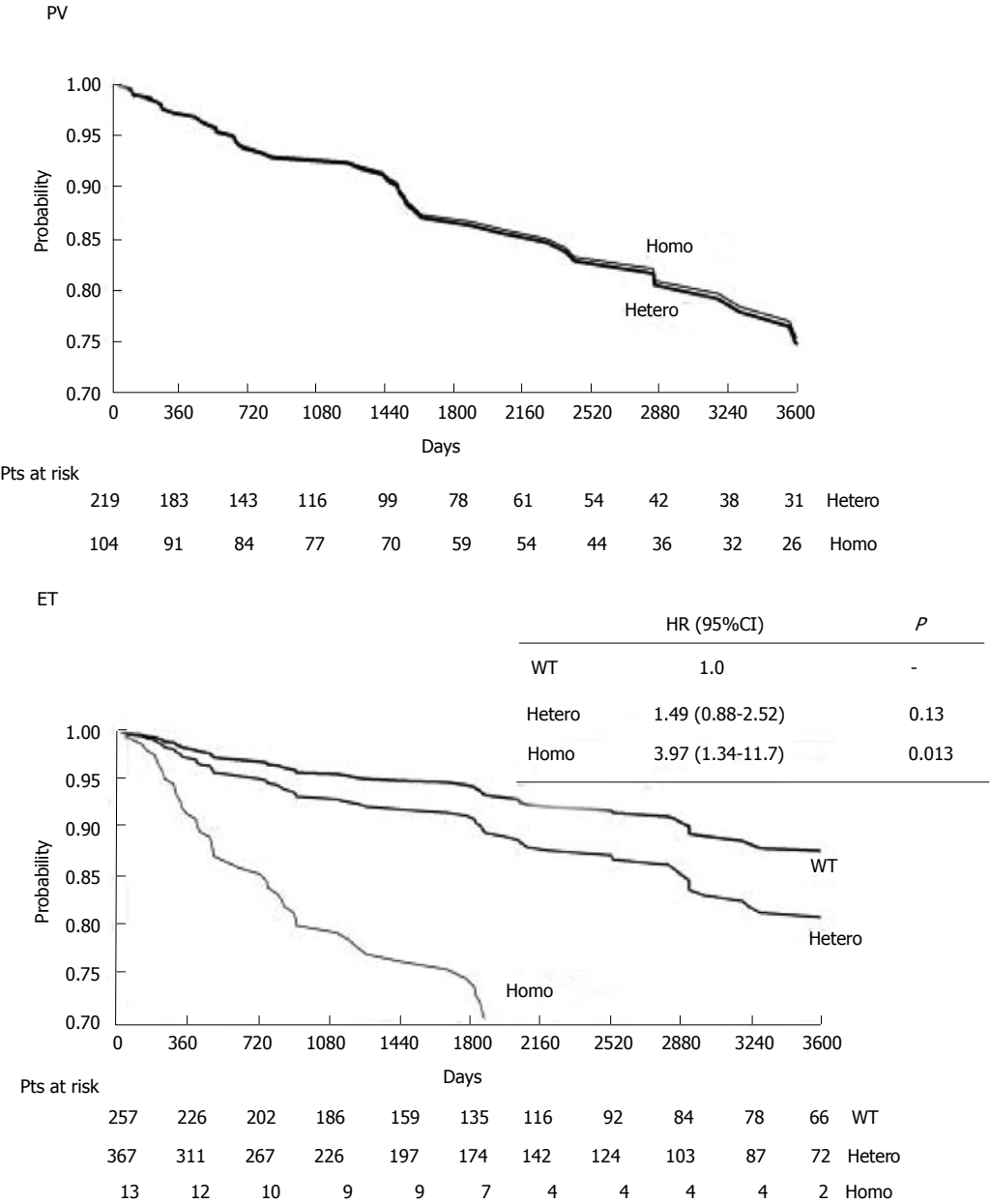


Figure 2 Retrospective study on the probability of cardiovascular thrombotic event-free survival (days up to 3600 d = 10 years) according to the JAK2^{V617F} mutational state in 323 polycythemia vera and 639 essential thrombocythemia patients (Vannucchi *et al*^[20]). Only major thrombotic events were retrospectively recorded and the erythromelalgic peripheral, ocular and cerebral ischemic events were excluded from evaluation. The overall incidence of major thrombotic events in JAK2^{V617F} mutated PV patients during 10 years follow-up is about 25% in the Italian study^[20]. A similar incidence of thrombotic events was found in our literature analysis of 1241 ET patients not on aspirin from 14 retrospective studies^[22]. Source Vannucchi *et al*^[20] Blood 2007. ET: Essential thrombocythemia; PV: Polycythemia vera.

at diagnosis manifested in 55 (5.7%) patients, 5.3% in PV and 6.0% in ET^[20]. The overall incidence of major thrombotic events during 10 years follow-up usually not on aspirin was about 20% in ET heterozygous for the JAK2^{V617F} mutation and in about 10% for JAK2 wild type ET^[20]. Hemorrhages during follow-up was recorded in 45 (4.7%) ET/PV patients. A similar incidence of hemorrhages was found in our analysis of the literature in 1241 ET patients from 14 retrospective studies^[22]. The frequency of bleeding was higher in JAK2^{V617F} homozygous (21.4%) than in wild type or heterozygous ET patients, 3.1% and 3.8% respectively. The higher bleeding tendency in homozygous JAK2^{V617F} MPN-T

patients is predicted to be related to higher erythrocyte counts at increased platelet and leukocyte counts and its pathophysiology of the underlying mechanisms is currently under our investigation^[10].

CLINICAL SYMPTOMS AND DIAGNOSIS IN 497 DUTCH MPN PATIENTS

The results from the 2008 MPN Questionnaires of the Dutch MPN Patient Foundation are the reflection of ECMP criteria for the diagnosis, classification and staging of MPN and treatment recommendations of ET

Table 4 Major cardiovascular and venous thrombotic events at diagnosis or during long-term follow-up in 323 polycythemia vera and 639 essential thrombocythemia patients according to the JAK2^{V617F} mutation status in the retrospective study of Vannucchi (only major thrombotic events were retrospectively recorded excluding the erythromelalgic and migraine like cerebral ischemic events^[20])

Patients	PV n = 323		ET n = 625	
JAK2 ^{V617}	Hetero homozygous hetero wild type			
mutation status				
No. of patients	219	104	368	237
At diagnosis				
Major arterial events	21%	15.4%	21.7%	10.5%
Venous events	2.9%	2.9%	7.9%	4.7%
During 10 yr follow-up (not on aspirin)				
Major arterial events	10.1%	12.5%	6.3%	5.8%
Venous events	4.1%	7.7%	6.3%	2.7%
Total during life time follow-up				
Major arterial	31.1%	27.9%	28%	16.3%
Venous	10.5%	10.6%	14.2%	7.4%

In 14 homozygous ET patients total major arterial and venous events had occurred in 78.6% and 57.1% respectively. PV: Polycythemia vera; ET: Essential thrombocythemia.

and PV patients in The Netherlands between 2000 and 2008^[13,23,24]. Low dose aspirin in ET and phlebotomy on top of aspirin is effective in the majority of ET and in two third of PV patients with low or mild MPN disease burden. Low dose pegylated interferon is recommended in PV with mild to moderately increased MPN disease like leukocytosis, itching and mild to moderate splenomegaly to postpone hydroxyurea. The collected Dutch MPN data were published in PUR SANG in 2010 based on 497 filled forms by MPN patients: 271 females (54%) and 212 males (43%), mean age at diagnosis 57 years (range 20 to 84 years)^[23]. The diagnoses of 497 MPN patients were ET in 181 (36%), PV in 244 (50% of whom 18 as ET/PV), MF in 67 (13%), and MPN unclassifiable in 5 (1%). The detection of MPN disease 115 Dutch and Belgian hospitals was related to MPN specific complaints in 55%, coincidental (*e.g.*, routine laboratory investigation for other reasons) in 30% and after significant delay of disease specific complications 15%. Diagnosis of MPN was confirmed by bone marrow investigations in 475 (96%) of 497 MPN patients^[23]. Red cell mass (RCM) measurement to diagnose PV and to distinguish ET from PV was performed in 31%. PCR test for the JAK2^{V617F} mutation anno 2008 was performed in 230 (46%) MPN patients and found positive in 74% (ET *n* = 52, PV *n* = 103, MF *n* = 14) and negative in 26%. Sixty percent of ET, 91% of PV and 52% of MF patients were JAK2^{V617F} positive, thereby confirming the data in the literature. After primary diagnosis 144 (25%) MPN patients (ET *n* = 38, PV *n* = 49, MF *n* = 27) were referred for a second opinion. The second expert evaluation led to a change in diagnosis in 8% and a change in treatment in 28% (*n* = 29). The second treatment option in 29 (28%) proved to be superior to the initial treatment. A change of diagnosis during

follow-up occurred in 60 MPN patients, from ET into PV in 16 (9% of PV), from PV into MF in 15 (6% of PV), and from ET into MF in 10 (6% of ET)^[23].

MPN RELATED SIGNS AND SYMPTOMS IN 497 DUTCH ET, PV AND MF PATIENTS

Based on the Dutch MPN questionnaire including 36 questions the top 20 complaints at time of diagnosis in 399 out of 497 (81%) MPN patients is shown in Table 5^[23]. The most frequent complaint is fatigue (81%) equally high in ET, PV and MF patients. Apart from variable severity of fatigue a specific pattern of signs and symptoms could be retrieved. The signs and symptoms in ET are mainly featured by aspirin responsive tingling and prickling sensations in footsoles, hand palms, toes and fingers (erythromelalgia), and aspirin responsive cognitive concentration and visual disturbances (Table 5). PV patients presented with similar signs and symptoms but on top of that both aspirin resistant itching (PV 58% vs ET 30%) and fatigue were much more prominent in PV. A second most frequent complaint were various degrees of night sweats related to splenomegaly in about half of the MPN patients. About one third of MPN patients suffered from bone pain (Table 5). MF patients suffered more frequently from constitutional symptoms of prominent fatigue and night sweats related to pronounced splenomegaly. Before the MPN diagnosis was made the complaints were ascribed by doctors in 173 (35%) patients to other causes including stress, burned out or overstrained in 41 (24%), to depression or hysteria in 14 (8%), migraine of unknown origin (and therefore not treated with aspirin) in 13 (8%) and to rheuma, hypertension or fibromyalgia in a few^[23].

TREATMENT AND ADVERSE EVENTS IN DUTCH MPN PATIENTS 2003-2008

Treatment in 497 MPN patients was started with low dose aspirin or calcium carbasalate (Ascal) in 70% and phlebotomy in 42% (mainly PV 91%), hydroxyurea in 29%, and pegylated interferon-alpha2a in 7%, wait and see in 8% (*n* = 42 of whom 26 with MF) of MPN patients at time of diagnosis (Figure 3)^[23]. The treatment changed during follow-up in 294 (60%) of MPN patients: ET in 64% (*n* = 115), PV in 59% (*n* = 143) and MF in 49% (*n* = 33). Out of 459 evaluable adverse drug reactions or side effects were recorded in one third (*N* = 168 = 35%) of MPN patients. Out of the 168 recorded side effects were related to HU in 41% (*n* = 69) and to IFN in 28% (*n* = 47) of all side effects. Most frequent side effects of HU were skin and mucocutaneous complaints including dry skin, skin lesions, skin ulcers, itching, skin carcinoma, brittle nails, aphtous ulcers and hair loss, and most frequent side effects of IFN were flue-like symptoms, fatigue

Table 5 Top 20 clinical manifestations in patients with who defined myeloproliferative neoplasm essential thrombocythemia, polycythemia vera and myelofibrosis based on the Dutch myeloproliferative neoplasm Questionnaire 2009-2010^[23]

Symptom	Top 20 MPN complaints	All MPN <i>n</i> = 497	MPN %	ET %	PV %	MF %
1	Fatigue, listless	399	81	80	81	85
2	Microvascular acra ³⁷	278	57	61	56	46
3	Cognitive disturbances ³⁷	262	53	52	56	45
4	Visual disturbances ³⁷	249	51	50	52	46
5	Night sweats	236	48	44	50	52
6	Itching	220	45	30	58	36
7	Dizziness	218	44	44	46	39
8	Bruises, bleedings	211	43	40	45	43
9	Splenomegaly constitutional symptoms	198	40	22	43	78
10	Tinnitus	188	38	38	39	37
11	Migraine headache without visual symptoms	184	37	46	35	22
12	Bone pain	172	35	33	36	34
13	Heart arrhythmias	154	31	34	31	24
14	Dysarthria, dyslexia	151	31	31	31	30
15	Hypersensitive to sounds and noises	149	30	29	32	28
16	Paleness	145	29	30	26	40
17	Claudication intermittens	140	28	28	30	24
18	Hypersensitive to lights	136	28	25	32	16
19	Visual disturbances without headache	18	33	54	3	90
20	Headache without visual symptoms	24	43	43	4	90

Microvascular acra: Tingling, prickling sensations, redness, swelling and/or bluish discolouration of footsoles, handpalms, toes and/or fingers³⁷. Cognitive disturbances of concentration and memory and sudden attacks of unconscieness. Visual disturbances of scintillating scotomas, light flashes, blurred vision, transient monocular blindness, rapid spreading of visual figure disturbances³⁷. Attacks of migraine-like headaches followed by nausea or vomiting or loss of consciencous or transient paresis of one extremity³⁷. MPN: Myeloproliferative neoplasm; ET: Essential thrombocythemia; PV: Polycythemia vera; MF: Myelofibrosis.

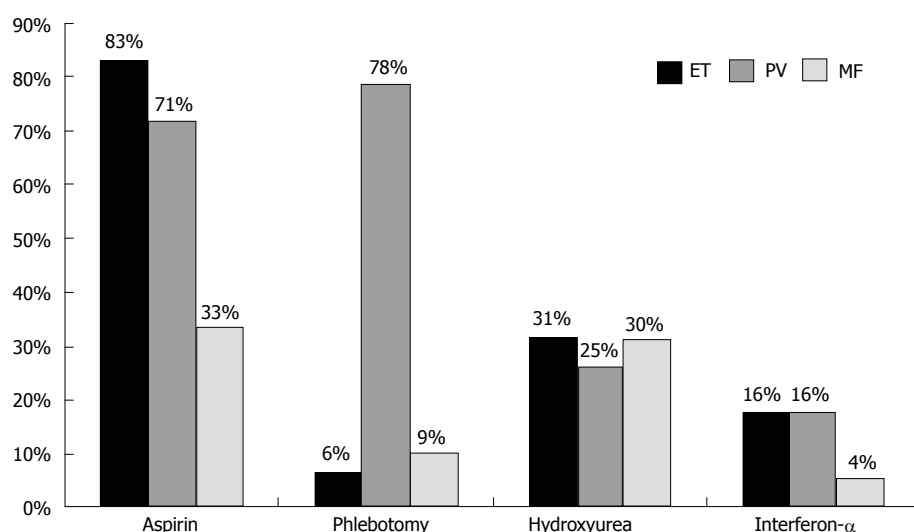


Figure 3 Mode of treatment in the Dutch 2008 survey of 363 myeloproliferative neoplasm (123 essential thrombocythemia, 190 polycythemia vera and 50 myelofibrosis) patients: 93% of polycythemia vera, 71% of essential thrombocythemia and 37% of myelofibrosis were on aspirin; 6% of essential thrombocythemia, 78% of polycythemia vera and 9% of myelofibrosis were treated with phlebotomy^[23]. Because of symptomatic MNP disease burden 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET, 16% of PV and 4% of MF were on treatment with pegylated interferon (Pegasys)^R^[23]. ET: Essential thrombocythemia; PV: Polycythemia vera; MF: Myelofibrosis; MNP: Myeloproliferative neoplasm.

and mood disturbances^[23]. Low dose aspirin or Ascal induced gastritic complaints in 11% for which treatment with metronidazol was usually indicated^[23].

DISCUSSION

In the Dutch 2008 survey of 363 MPN (123 ET, 190 PV and 50 MF) patients 93% of PV, 71% of ET and 37%

of MF were on aspirin mainly because of microvascular symptoms including migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances. Phlebotomy became the first line treatment in 6% of ET, 78% of PV and 9% of MF^[23]. Because of advanced or symptomatic MPN disease 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET and PV and

Table 6 Staging of JAK2^{V617F} positive prodromal polycythemia vera, erythrocythemic polycythemia vera, and five stages of PV according to WHO-ECMP criteria related to therapy anno 2014^[10,13,34-37]

PV: WHO-ECMP stage	0	1	2	3	4	5	6
WHO-ECMP	Prodromal PV	Erythrocythemic PV	Early PV	Overt PV	PV PMF	Post-PV MF	Leukemic PV
clinical diagnosis				Classical PV	Masked PV	Spent PV	MDS/AL
LAP-score	↑	↑	↑	↑	↑/↑↑	Variable	Variable
Red cell mass	N	↑	↑	↑	↑	Variable	N/↓
Serum EPO	N/↓	N/↓	↓	↓	↓	Variable	N/↓
Erythrocytes × 10 ¹² /L	< 5.8	> 5.8	> 5.8	> 5.8	< 5.8	Variable	N/↓
Leukocytes × 10 ⁹ /L	< 12	< 12	< or > 12	< or > 15	> 15	> 20	> 20
Platelets × 10 ⁹ /L	> 400	400	< or > 400	> 400	< or > 1000	Variable	Variable
WHO-ECMP bone marrow	Early PV	Early PV	Early PV	Trilinear PV	Trilinear PV	Myelofibrosis	Leukemic
Bone marrow cellularity (%)	50-80	50-80	60-100	80-100	80-100	Decreased	Increased
Grading reticulin fibrosis: RF	RF 0-1	RF 0-1	RF 0-1	RF 0/1,	RCF 2/3	RCF 3/4	
Grading myelofibrosis: MF ⁵⁷	MF 0	MF 0	MF 0	MF 0	MF 1/2	MF 2/3	
Splenomegaly on palpation	No/+	No	No/+	+	++/+++	/Large	Large
Spleen size, echogram cm	< 12-15	< 13	12-15	12-18	18 - > 20	> 20	> 20
Spleen size on palpation cm	0-3	NP	0-3	4-6	> 6	> 8	> 8
JAK2 ^{V617F} in Granulocytes %	low	low	Moderate < 50	High > 50	High > 50	High > 50	No or ++
JAK2 ^{V617F} in BFU-e (exon 12)	+(++)	+(++)	+(++)	++	++	++	
Therapeutic implications	Low risk	Low risk	Low risk	Intermediate risk PV	High risk PV-MF	Post-PV MF	Leukemia
Anno 2014						Spent phase PV	
First line aspirin/Phlebotomy	Aspirin	Aspirin	Phlebotomy	Phlebotomy ¹	If IFN resistant	JAK2	Chemotherapy
Second line IFN vs HU	Phlebotomy	Phlebotomy	Aspirin	Aspirin	→	Inhibitor →	Bone marrow transplantation?
Third line JAK2 inhibitor			Low dose IFN → responsive	IFN à resistant → HU	HU or JAK2 inhibitor	Bone marrow transplantation	Supportive

↑: Increased; ↓: Decreased; N: Normal; +: Present or heterozygous; ++: Homozygous; HU: Hydroxyurea; PV: Polycythemia vera; MF: Myelofibrosis; WHO-ECMP: World Health Organization and European Clinical Molecular and Pathological; LAP: Leukocyte alkaline phosphatase; EPO: Erythropoietin.

4% of MF were on treatment with pegylated interferon (Pegasys[®]). In the study of Vannucchi *et al*^[20], a total of 214 patients were treated with phlebotomy, 58% of 219 PV and 4% of 257 ET patients. Myelosuppressive chemotherapy was administered to 497 patients (52%) including 59% of 219 PV and 48% of 257 ET patients. The 20% difference of HU use (50% of Italian MPN-T patients vs 30% of Dutch MPN-T patients) can readily be ascribed to significant differences in the Italian vs the Dutch guidelines for MPN-T disease in ET and PV patients. MPN-T patients in the Netherlands were treated according to the 2000 guidelines for ET and PV^[13]. Low risk MPN-T disease in ET and PV patients at ages 18 to 80 years is defined by platelet count < 1500 × 10⁹/L, absence of vascular risk factors like hypertension, hypercholesterolemia, diabetes atherosclerosis and absence of bleeding complications. First line treatment option in MPN-T disease in ET and PV patients followed the published Dutch guidelines since 2000^[6-10]. If asymptomatic, no microvascular symptoms and no major thrombosis like minor stroke of myocardial infarction low dose aspirin 40 mg a day is given in JAK2^{V617F} mutated MPN-T. Symptomatic MPN-T patients including migraine atypical TIAs, minor TIAs, low back pain, painful toes or fingers, and major thrombosis were treated low dose aspirin. When MPN-T is associated with leukocytosis, moderate splenomegaly or platelet count above 1000 × 10⁹/L low dose Pegasys 45 µg/mL will become the treatment of choice in JAK2^{V617F} mutated ET and PV. At age above 70 freedom to choose hydroxyurea or low dose pegasys must

prevail. Please note that these are general Dutch MPN-T treatment guidelines, which has to be discussed with the local hematologist or internist for approval^[22-26].

The 2013 WHO-ECMP criteria clearly define and stage the JAK2^{V617F} defined MPN entity of prodromal PV, prefibrotic PV, early fibrotic PV, PV complicated by myelofibrosis (post-PV MF), significant myeloid metaplasia of the spleen with splenomegaly and related constitutional symptoms (Table 6)^[13]. Within the JAK2^{V617F} MPN phenotypes, the JAK2^{V617F} mutated hypercellular ET is associated with clustered pleiomorphic megakaryopoiesis, increased granulopoiesis and relative decrease of erythropoiesis without a documented history of ET or PV. The integrated WHO-CMP criteria surely will have important implications in choosing proper targeted treatment options for the prevention of thrombotic and bleeding complications in prodromal PV and PV and for the management of serious complications of progressive MPN disease burden requiring myeloreductive treatment with pegylated interferon (Pegasys[®]) and if non-responsive or side effects low dose hydroxyurea to correct increased blood cell counts in overt and advanced PV patients (Table 6)^[10,13]. Venesection aiming at a hematocrit below 0.45 in males and below 0.42 in females is the first line treatment option in PV patients^[24-29]. Phlebotomy aiming more strictly at a hemotocrit of less than 0.40 and a MCV of less than 70 fl in males and females on top of well controlled low dose aspirin in PV patients will significantly reduce the cumulative incidence of major thrombosis, but the microvascular syndrome of associated thrombocythemia

persist when not on aspirin^[13]. According to current insights, low dose interferon is the treatment of choice in intermediate stage PV patients (Figure 1, Table 6)^[13,30-33]. If not responsive to IFN or side effects induced by IFN, hydroxyurea is the second line myelosuppressive treatment option in JAK2^{V617F} mutated ET and PV patients (Table 6). Hydroxyurea is not an innocent drug and should be used with caution (Table 6). The final analysis of the 1980 French PVSG study of HU as upfront therapy at time of diagnosis in 136 evaluable PV patients younger than 65 years is published in 2011^[32]. The cumulative incidence (probability) of myelofibrosis (MF) at 10, 15 and 20 years was 15%, 24% and 32% in the HU arm and the cumulative incidence of AML/MDS at 10, 15 and 20 years was 7.3%, 10.7% and 16.6% for HU treated PV patients. Proper staging of PV in terms of JAK2^{V617F} mutation load, and MPN disease burden by measuring the degree of splenomegaly and severity of constitutional symptoms including itching on top of bone marrow histology and grading of fibrosis is of huge importance since it has significant implications for a non-leukemogenic or the least potential leukemogenic treatment options in low, intermediate and high risk PV patients (Figure 1, Table 6)^[10,34-37]. As shown in Table 6, high risk PV and MF patients with advanced MPN-T disease in terms of high JAK2^{V617F} allele burden, progressive MPN disease with splenomegaly and constitutional symptoms are candidates for myelo-suppressive (hydroxyurea) or myeloreductive (JAK2 inhibitors) treatment^[10,34-37].

REFERENCES

- 1 Michiels JJ. Erythromelalgia and thrombocythemia: Thesis Rotterdam. Rotterdam: Erasmus University Rotterdam, 1981
- 2 van Genderen PJ, Michiels JJ. Erythromelalgic, thrombotic and haemorrhagic manifestations of thrombocythaemia. *Presse Med* 1994; **23**: 73-77 [PMID: 8140075]
- 3 Michiels JJ, Abels J, Steketee J, van Vliet HH, Vuzevski VD. Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. *Ann Intern Med* 1985; **102**: 466-471 [PMID: 3977194 DOI: 10.7326/0003-4819-102-4-466]
- 4 Van Genderen PJ, Michiels JJ. Hydroxyurea in essential thrombocytosis. *N Engl J Med* 1995; **333**: 802-803 [PMID: 7643898 DOI: 10.1056/NEJM199509213331216]
- 5 van Genderen PJ, Mulder PG, Waleboer M, van de Moedijk D, Michiels JJ. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. *Br J Haematol* 1997; **97**: 179-184 [PMID: 9136963 DOI: 10.1046/j.1365-2141.1997.d01-2127.x]
- 6 Michiels JJ. Aspirin and platelet-lowering agents for the prevention of vascular complications in essential thrombocythemia. *Clin Appl Thromb Hemost* 1999; **5**: 247-251 [PMID: 10726022 DOI: 10.1177/107602969900500408]
- 7 Michiels JJ. Normal life expectancy and thrombosis-free survival in aspirin treated essential thrombocythemia. *Clin Appl Thromb Hemost* 1999; **5**: 30-36 [PMID: 10725980]
- 8 van Genderen PJ, Michiels JJ, van der Poel-van de Luytgaarde SC, van Vliet HH. Acquired von Willebrand disease as a cause of recurrent mucocutaneous bleeding in primary thrombocythemia: relationship with platelet count. *Ann Hematol* 1994; **69**: 81-84 [PMID: 8080884 DOI: 10.1007/BF01698487]
- 9 Michiels JJ. Erythromelalgia and vascular complications in polycythemia vera. *Semin Thromb Hemost* 1997; **23**: 441-454 [PMID: 9387203 DOI: 10.1055/s-2007-996121]
- 10 Michiels JJ, Ten Kate FWJ, Koudstaal PJ, Van Genderen PJ. Aspirin responsive platelet thrombophilia in essential thrombocythemia and polycythemia vera. *World J Hematol* 2013; **2**: 20-43 [DOI: 10.5315/wjh.v2.i2.20]
- 11 Cortelazzo S, Viero P, Finazzi G, D'Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. *J Clin Oncol* 1990; **8**: 556-562 [PMID: 2307991]
- 12 Michiels JJ, van Genderen PJ, Lindemans J, van Vliet HH. Erythromelalgic, thrombotic and hemorrhagic manifestations in 50 cases of thrombocythemia. *Leuk Lymphoma* 1996; **22** Suppl 1: 47-56 [PMID: 8951772]
- 13 Michiels JJ, Berneman Z, Schroyens W, Hebeda K, Bot F, Lam KH, De Raeve H. PVSG and the WHO versus the European Clinical, Molecular and Pathological (ECMP) criteria for the diagnosis, classification and staging of the myeloproliferative neoplasms. *World J Hematol* 2013; **2**: 71-90 [DOI: 10.5315/wjh.v2.i3.71]
- 14 Passamonti F, Thiele J, Girodon F, Rumi E, Carobbio A, Gisslinger H, Kvasnicka HM, Ruggeri M, Randi ML, Gangat N, Vannucchi AM, Gianatti A, Gisslinger B, Müllauer L, Rodeghiero F, d'Amore ES, Bertozzi I, Hanson CA, Boveri E, Marino F, Maffioli M, Caramazza D, Antonioli E, Carrai V, Buxhofer-Ausch V, Pascutto C, Cazzola M, Barbui T, Tefferi A. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. *Blood* 2012; **120**: 1197-1201 [PMID: 22740446 DOI: 10.1182/blood-2012-01-403279]
- 15 Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, Barbui T. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med* 1995; **332**: 1132-1136 [PMID: 7700286 DOI: 10.1056/NEJM199504273321704]
- 16 Scott LM, Scott MA, Campbell PJ, Green AR. Progenitors homozygous for the V617F mutation occur in most patients with polycythemia vera, but not essential thrombocythemia. *Blood* 2006; **108**: 2435-2437 [PMID: 16772604 DOI: 10.1182/blood-2006-04-018259]
- 17 Moliterno AR, Williams DM, Rogers O, Isaacs MA, Spivak JL. Phenotypic variability within the JAK2 V617F-positive MPD: roles of progenitor cell and neutrophil allele burdens. *Exp Hematol* 2008; **36**: 1480-1486 [PMID: 18723264 DOI: 10.1016/j.exphem.2008.05.006]
- 18 Godfrey AL, Chen E, Pagano F, Ortmann CA, Silber Y, Bellosillo B, Guglielmelli P, Harrison CN, Reilly JT, Stegelmann F, Bijou F, Lippert E, McMullin MF, Boiron JM, Döhner K, Vannucchi AM, Besses C, Campbell PJ, Green AR. JAK2V617F homozygosity arises commonly and recurrently in PV and ET, but PV is characterized by expansion of a dominant homozygous subclone. *Blood* 2012; **120**: 2704-2707 [PMID: 22898600 DOI: 10.1182/blood-2012-05-431791]
- 19 Vannucchi AM, Antonioli E, Guglielmelli P, Longo G, Pancrazzi A, Ponziani V, Bogani C, Ferrini PR, Rambaldi A, Guerini V, Bosi A, Barbui T. Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. *Leukemia* 2007; **21**: 1952-1959 [PMID: 17625606 DOI: 10.1038/sj.leu.2404854]
- 20 Vannucchi AM, Antonioli E, Guglielmelli P, Rambaldi A, Barosi G, Marchioli R, Marfisi RM, Finazzi G, Guerini V, Fabris F, Randi ML, De Stefano V, Caberlon S, Tafuri A, Ruggeri M, Specchia G, Liso V, Rossi E, Pogliani E, Gugliotta L, Bosi A, Barbui T. Clinical profile of homozygous JAK2 617V > G mutation in patients with polycythemia vera or essential thrombocythemia. *Blood* 2007; **110**: 840-846 [PMID: 17379742 DOI: 10.1182/blood-2006-12-064287]
- 21 Rumi E, Pietra D, Ferretti V, Klampfl T, Harutyunyan AS, Milosevic JD, Them NC, Berg T, Elena C, Casetti IC, Milanese C, Sant'antonio E, Bellini M, Fugazza E, Renna MC, Boveri E, Astori C, Pascutto C, Kralovics R, Cazzola M. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood* 2014; **123**: 1544-1551 [PMID: 24366362]
- 22 Griesshammer M, Bangerter M, van Vliet HH, Michiels JJ.

- Aspirin in essential thrombocythemia: status quo and quo vadis. *Semin Thromb Hemost* 1997; **23**: 371-377 [PMID: 9263354 DOI: 10.1055/s-2007-996111]
- 23 Commandeur S. 500 MPD-ers onder de loep. Resultaten MPD enquête. *Pur Sang* 2010; **7**: 12-15
- 24 Michiels JJ, Barbui T, Finazzi G, Fuchtmann SM, Kutti J, Rain JD, Silver RT, Tefferi A, Thiele J. Diagnosis and treatment of polycythemia vera and possible future study designs of the PVSG. *Leuk Lymphoma* 2000; **36**: 239-253 [PMID: 10674896 DOI: 10.3109/10428190009148845]
- 25 Michiels JJ, Schouten HC. Artsenbrochure Myeloproliferative Disorders (MPD) Essentieel. Thrombocythemia, Polycythemia Vera Chronische Idiopathische Myelofibrose. Nederlandse MPD Stichting, 2006
- 26 Commendeur S, Michiels JJ, te Boekhorst PAW, Schouten HC, Zweegman S. Quality of life, social activity and work participation of MPD patients in The Netherlands: a survey of 363 MPD patients. Dutch: The Dutch MPD Foundation, 2008
- 27 Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. *Lancet* 1978; **2**: 1219-1222 [PMID: 82733 DOI: 10.1016/S0140-6736(78)92098-6]
- 28 Pearson TC. Diagnosis and classification of erythrocytoses and thrombocythoses. *Bailliere's Clin Haematol* 1998; **11**: 695-720 [DOI: 10.1016/S0950-3536(98)80035-8]
- 29 Messinezy M, Westwood NB, El-Hemaidi I, Marsden JT, Sherwood RS, Pearson TC. Serum erythropoietin values in erythrocytoses and in primary thrombocythaemia. *Br J Haematol* 2002; **117**: 47-53 [PMID: 11918532 DOI: 10.1046/j.1365-2141.2002.03386.x]
- 30 Najean Y, Rain JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. *Blood* 1997; **90**: 3370-3377 [PMID: 9345019]
- 31 Kiladjian JJ, Chevret S, Dosquet C, Chomienne C, Rain JD. Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. *J Clin Oncol* 2011; **29**: 3907-3913 [PMID: 21911721 DOI: 10.1200/JCO.2011.36.0792]
- 32 Kiladjian JJ, Cassinat B, Turlure P, Cambier N, Roussel M, Bellucci S, Menot ML, Massonnet G, Dutel JL, Ghomari K, Rousselot P, Grange MJ, Chait Y, Vainchenker W, Parquet N, Abdelkader-Aljassem L, Bernard JF, Rain JD, Chevret S, Chomienne C, Fenaux P. High molecular response rate of polycythemia vera patients treated with pegylated interferon alpha-2a. *Blood* 2006; **108**: 2037-2040 [PMID: 16709929]
- 33 Mullally A, Brueedigam C, Poveromo L, Heidel FH, Purdon A, Vu T, Austin R, Heckl D, Breyfogle LJ, Kuhn CP, Kalaitzidis D, Armstrong SA, Williams DA, Hill GR, Ebert BL, Lane SW. Depletion of Jak2V617F myeloproliferative neoplasm-propagating stem cells by interferon- α in a murine model of polycythemia vera. *Blood* 2013; **121**: 3692-3702 [PMID: 23487027 DOI: 10.1182/blood-2012-05-432989]
- 34 Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, Catalano JV, Deininger M, Miller C, Silver RT, Talpaz M, Winton EF, Harvey JH, Arcasoy MO, Hexner E, Lyons RM, Paquette R, Raza A, Vaddi K, Erickson-Viitanen S, Koumenis IL, Sun W, Sandor V, Kantarjian HM. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med* 2012; **366**: 799-807 [PMID: 22375971 DOI: 10.1056/NEJMoa1110557]
- 35 Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, McQuitty M, Hunter DS, Levy R, Knoops L, Cervantes F, Vannucchi AM, Barbui T, Barosi G. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med* 2012; **366**: 787-798 [PMID: 22375970 DOI: 10.1056/NEJMoa1110556]
- 36 Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, Mesa R, He S, Jones MM, Garrett W, Li J, Pirron U, Habr D, Verstovsek S. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med* 2015; **372**: 426-435 [PMID: 25629741 DOI: 10.1056/NEJMoa1409002]
- 37 Michiels JJ, Berneman Z, Schroyens W, De Raeve H. Changing concepts of diagnostic criteria of myeloproliferative disorders and the molecular etiology and classification of myeloproliferative neoplasms: from Dameshek 1950 to Vainchenker 2005 and beyond. *Acta Haematol* 2015; **133**: 36-51 [PMID: 25116092 DOI: 10.1159/000358580]

P- Reviewer: Boucek C, Kriebardis AG S- Editor: Ji FF

L- Editor: A E- Editor: Wu HL



Intensive care organisation: Should there be a separate intensive care unit for critically injured patients?

Tim K Timmers, Michiel HJ Verhofstad, Luke PH Leenen

Tim K Timmers, Luke PH Leenen, Department of Surgery, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands

Michiel HJ Verhofstad, Department of Surgery, Erasmus Medical Center Rotterdam, 3000 CA Rotterdam, The Netherlands

Author contributions: Timmers TK designed the research; Timmers TK and Leenen LPH performed the research; Timmers TK, Verhofstad MHJ and Leenen LPH wrote the paper.

Conflict-of-interest statement: The authors declared that they have no competing interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Tim K Timmers, MD, PhD, Department of Surgery, University Medical Center Utrecht, P.O.-box 85500, 3508 GA Utrecht, The Netherlands. tk.timmers@gmail.com
Telephone: +31-88-7559882
Fax: +31-88-7555555

Received: December 20, 2014
Peer-review started: December 21, 2014
First decision: February 7, 2015
Revised: March 12, 2015
Accepted: April 27, 2015
Article in press: April 29, 2015
Published online: August 4, 2015

Abstract

In the last two decennia, the mixed population general intensive care unit (ICU) with a "closed format" setting has gained in favour compared to the specialized critical

care units with an "open format" setting. However, there are still questions whether surgical patients benefit from a general mixed ICU. Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requiring immediate surgical intervention and/or intensive care treatment. The role and type of the ICU has received very little attention in the literature when analyzing outcomes from critical injuries. Severely injured patients require the years of experience in complex trauma care that only a surgery/trauma ICU can provide. Should a trauma center have the capability of a separate specialized ICU for trauma patients ("closed format") next to its standard general mixed ICU?

Key words: Intensive trauma care; Trauma intensive care; Critical care; Intensive care medicine; Trauma

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requires immediate surgical intervention and/or intensive care treatment. Severely injured patients require the years of experience in complex trauma care that only a surgery/trauma intensive care unit can provide.

Timmers TK, Verhofstad MHJ, Leenen LPH. Intensive care organisation: Should there be a separate intensive care unit for critically injured patients? *World J Crit Care Med* 2015; 4(3): 240-243 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/240.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.240>

INTRODUCTION

The contribution of organizational structure - in a wide variety of settings - for the delivery of critical care to patients has been the topic of study since the mid-

1980s^[1-9]. The preponderance of evidence recommends that intensivist-directed patient management is related to a reduced length of intensive care unit (ICU) stay, reduced hospital length of stay, and most likely decreased mortality. In the last two decennia, the mixed population general ICU with a “closed format” setting has gained in favour compared to the specialized critical care units with an “open format” setting, especially in Europe^[8-15]. Therefore, critical care physicians have taken responsibility for the treatment of critically ill patients, and more and more specialized units are embedded in the intensive care department. These units are subsequently transformed into overall general units with a mixed population of different diseases. Although there seems to be more positive results towards the general mixed ICU within a “closed format” setting in the literature^[4,6-8,10,16-23], there are still questions whether surgical patients benefit from a general mixed ICU. The only evidence accessible on this field comes from the neurosurgical intensive care; Intracerebral hemorrhage patients treated in a specialized neuroscience ICU had lower mortality, length of stay, and cost than those treated in a general ICU^[24,25]; and from the burn intensive care^[26-29]. Does this mean that we have to reorganise all specialized surgical units, even if those units are already working in accordance with the “closed format” setting? Several authors state that we should not reform all of our specialized surgical ICUs^[30-33].

Trauma has been called the unnoticed epidemic and the unheeded disease of modern society. Trauma every year impacts hundreds of thousands of individuals and cost billions of dollars in direct financial loss^[34]. Trauma care has improved over the past 20 years, largely from improvements in trauma systems, assessment, triage, resuscitation, emergency and intensive care^[34]. Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requires immediate surgical intervention and/or intensive care treatment. Over one quarter of trauma patients are cared for in an ICU during their hospital admission in the United States^[33,35]. Modern trauma care has become highly specialized, especially for the critically ill patient with multiple-system injuries^[36]. The care provided in this setting plays a major role in ensuring survival following injury and might significantly influence functional outcome^[33]. Nevertheless, the function and structure of the ICU has received very little awareness in the literature when examining outcomes from critical injuries^[36]. The American College of Surgeons Committee on Trauma, whose criteria is used for the verification of trauma centers, recommends that the surgeon presuming first responsibility for the care of the injured patient should maintain that responsibility all through the acute care phase of hospitalization, including the ICU^[37]. Nathens *et al*^[30] have concluded that closed ICUs with a surgeon intensivist had the best outcome in the care of the critically injured trauma patient compared with the non-surgeon intensivists. Park *et al*^[32] suggested that improved clinical outcomes, lower costs and reduced

length of stay are directly related to a separate closed trauma unit. And the most recent study of Duane *et al*^[36] concludes that severely injured patients require the years of experience in complex trauma care that only a surgery/trauma ICU can organise. These patients air a number of exceptional challenges for the ICU physician including the need for ongoing resuscitation, drive of resuscitation endpoints, and treatment of early post-resuscitation complications. How well these are addressed may have critical implications for long-term outcome and survival^[38]. Timing in treatment (especially re-operations in the first 48 h) of the critically injured patient is of great importance; and who is better to understand these circumstances than the surgeon intensivist (with experience in trauma surgery)? In a perfect world, should a trauma center have the capability of a separate specialized ICU for trauma patients (“closed format”) next to its standard general mixed ICU? Critically injured patients requiring admission to the ICU often have multi-system injuries that require technically advanced medicine including resuscitation from shock. The ICU care of the trauma patient differ from that of other intensive care patients in many ways, one of the most important being the need to continuously combine operative and non-operative treatment. Though, development in the care of the injured has been made, death due to uncontrolled bleeding, severe head injury, or the development of multiple organ dysfunction syndrome remains all too common in this patient population. Additionally, due to the potential nature of the injuries, the problem not seldom arises that the optimum therapy for one injury or organ system, such as preoperative permissive hypotension in actively bleeding patients, may result in suboptimal or even harmful therapy in the existence of an other injury (such as traumatic brain injury)^[39]. In addition, trauma leads to a state of relative immunosuppression with decreased humoral and cell mediated immunity^[40-45].

Trauma surgery critical care teams often consult multiple specialists to provide the complex care necessary to treat the most severely injured. It is true that this kind of advanced medicine is indeed available at each Level I trauma center general ICU. However, would the experience of highly trained personnel (trauma nurses, senior surgical residents, trauma fellows) contribute even more to a better patient outcome? With this kind of highly trained and experience personnel the possibility exists to perform small operations on the unit itself without having to wait and transport the critically injured patient to an operation theatre. Complex, high skilled nursing interventions such as volume replacement, correction of coagulopathy and hypothermia, invasive monitoring and the management of “damage-control” conditions demand understanding and experience that are not able to be gauged. These skills are obtained on a daily basis in Trauma ICUs where there is an excess of “hands-on” learning possibility. The development of such skills is critical for optimal results in life-threatening

blunt and penetrating trauma. An identical care is hard to attain even from staff that is experienced and exceptional in their non-surgical fields^[36]. Even in our own intensive care patient organisation (concerning surgical patients and the critically injured patients on outcome), a difference in the dimensions of crude ICU outcome (short-term mortality/length of ICU stay and ICU readmission) was seen after the reorganization to a general ICU^[46]. Should there not be an organised survey among different trauma centers to analyse the critically injured patient outcome. This should give critical care physicians and surgeons specialized in trauma insight in the question whether patient outcome could gain from separate trauma units or give us the conclusive information whether we should continue combining all specialized care units together.

REFERENCES

- 1 Li TC, Phillips MC, Shaw L, Cook EF, Natanson C, Goldman L. On-site physician staffing in a community hospital intensive care unit. Impact on test and procedure use and on patient outcome. *JAMA* 1984; **252**: 2023-2027 [PMID: 6481908 DOI: 10.1001/jama.252.15.2023]
- 2 Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. *Chest* 1989; **96**: 127-129 [PMID: 2736969 DOI: 10.1378/chest.96.1.127]
- 3 Pronovost PJ, Jenckes MW, Dorman T, Garrett E, Breslow MJ, Rosenfeld BA, Lipsett PA, Bass E. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA* 1999; **281**: 1310-1317 [PMID: 10208147 DOI: 10.1001/jama.281.14.1310]
- 4 Ghorra S, Reinert SE, Cioffi W, Buczek G, Simms HH. Analysis of the effect of conversion from open to closed surgical intensive care unit. *Ann Surg* 1999; **229**: 163-171 [PMID: 10024095 DOI: 10.1097/0000658-199902000-00001]
- 5 Hanson CW, Deutschman CS, Anderson HL, Reilly PM, Behringer EC, Schwab CW, Price J. Effects of an organized critical care service on outcomes and resource utilization: a cohort study. *Crit Care Med* 1999; **27**: 270-274 [PMID: 10075049 DOI: 10.1097/00003246-199902000-00030]
- 6 Manthous CA, Amoateng-Adjepong Y, al-Kharrat T, Jacob B, Alnuaimat HM, Chatila W, Hall JB. Effects of a medical intensivist on patient care in a community teaching hospital. *Mayo Clin Proc* 1997; **72**: 391-399 [PMID: 9146680 DOI: 10.4065/72.5.391]
- 7 Reynolds HN, Haupt MT, Thill-Baharozian MC, Carlson RW. Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. *JAMA* 1988; **260**: 3446-3450 [PMID: 3210284 DOI: 10.1001/jama.1988.03410230064029]
- 8 Multz AS, Chalfin DB, Samson IM, Dantzker DR, Fein AM, Steinberg HN, Niederman MS, Scharf SM. A "closed" medical intensive care unit (MICU) improves resource utilization when compared with an "open" MICU. *Am J Respir Crit Care Med* 1998; **157**: 1468-1473 [PMID: 9603125 DOI: 10.1164/ajrccm.157.5.9708039]
- 9 Topeli A, Laghi F, Tobin MJ. Effect of closed unit policy and appointing an intensivist in a developing country. *Crit Care Med* 2005; **33**: 299-306 [PMID: 15699831 DOI: 10.1097/01.CCM.0000153414.41232.90]
- 10 Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002; **288**: 2151-2162 [PMID: 12413375 DOI: 10.1001/jama.288.17.2151]
- 11 Groeger JS, Strosberg MA, Halpern NA, Raphaely RC, Kaye WE, Guntupalli KK, Bertram DL, Greenbaum DM, Clemmer TP, Gallagher TJ. Descriptive analysis of critical care units in the United States. *Crit Care Med* 1992; **20**: 846-863 [PMID: 1597041 DOI: 10.1097/00003246-199206000-00024]
- 12 Schmitz R, Lantin M, White A. Future Workforce Needs in Pulmonary and Critical Care Medicine. Cambridge, Mass: Abt Associates, 1999
- 13 Audit Commission. Critical to Success: The Place of Efficient and Effective Critical Care Services Within the Acute Hospital. London, England: Audit Commission, 1999
- 14 Ferdinande P. Recommendations on minimal requirements for Intensive Care Departments. Members of the Task Force of the European Society of Intensive Care Medicine. *Intensive Care Med* 1997; **23**: 226-232 [PMID: 9069011 DOI: 10.1007/s001340050321]
- 15 Cole L, Bellomo R, Silvester W, Reeves JH. A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system. *Am J Respir Crit Care Med* 2000; **162**: 191-196 [PMID: 10903628 DOI: 10.1164/ajrccm.162.1.9907016]
- 16 Parrillo JE. A silver anniversary for the Society of Critical Care Medicine--visions of the past and future: the presidential address from the 24th Educational and Scientific Symposium of the Society of Critical Care Medicine. *Crit Care Med* 1995; **23**: 607-612 [PMID: 7712746 DOI: 10.1097/00003246-199504000-00001]
- 17 Flaatten H. Effects of a major structural change to the intensive care unit on the quality and outcome after intensive care. *Qual Saf Health Care* 2005; **14**: 270-272 [PMID: 16076791 DOI: 10.1136/qshc.2004.013540]
- 18 Fuchs RJ, Berenholtz SM, Dorman T. Do intensivists in ICU improve outcome? *Best Pract Res Clin Anaesthesiol* 2005; **19**: 125-135 [PMID: 15679063 DOI: 10.1016/S1521-6896(04)00050-3]
- 19 Pronovost PJ, Dang D, Dorman T, Lipsett PA, Garrett E, Jenckes M, Bass EB. Intensive care unit nurse staffing and the risk for complications after abdominal aortic surgery. *Eff Clin Pract* 2001; **4**: 199-206 [PMID: 11685977]
- 20 Leapfrog Group. ICU Physician Staffing Factsheet. Washington, DC: Leapfrog Group, 2004
- 21 Vincent JL. Need for intensivists in intensive-care units. *Lancet* 2000; **356**: 695-696 [PMID: 11085683 DOI: 10.1016/S0140-6736(00)02622-2]
- 22 Chittawatanarat K, Pamorsinlapathum T. The impact of closed ICU model on mortality in general surgical intensive care unit. *J Med Assoc Thai* 2009; **92**: 1627-1634 [PMID: 20043565]
- 23 Young MP, Birkmeyer JD. Potential reduction in mortality rates using an intensivist model to manage intensive care units. *Eff Clin Pract* 2000; **3**: 284-289 [PMID: 11151525]
- 24 Mirski MA, Chang CW, Cowan R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. *J Neurosurg Anesthesiol* 2001; **13**: 83-92 [PMID: 11294463 DOI: 10.1097/00008506-200104000-00004]
- 25 Dringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med* 2001; **29**: 635-640 [PMID: 11373434 DOI: 10.1097/00003246-200103000-00031]
- 26 Karyoute SM, Badran DH. Analysis of 100 patients with thermal injury treated in a new burn unit in Amman, Jordan. *Burns Incl Therm Inj* 1989; **15**: 23-26 [PMID: 2720452 DOI: 10.1016/0305-4179(89)90064-8]
- 27 Herndon DN, Spies M. Modern burn care. *Semin Pediatr Surg* 2001; **10**: 28-31 [PMID: 11172570 DOI: 10.1053/spsu.2001.19389]
- 28 Fagan SP, Bilodeau ML, Goverman J. Burn intensive care. *Surg Clin North Am* 2014; **94**: 765-779 [PMID: 25085087 DOI: 10.1016/j.suc.2014.05.004]
- 29 Snell JA, Loh NH, Mahambrey T, Shokrollahi K. Clinical review: the critical care management of the burn patient. *Crit Care* 2013; **17**: 241 [PMID: 24093225 DOI: 10.1186/cc12706]
- 30 Nathens AB, Rivara FP, MacKenzie EJ, Maier RV, Wang J, Egleston B, Scharfstein DO, Jurkovich GJ. The impact of an intensivist-model ICU on trauma-related mortality. *Ann Surg* 2006; **244**: 545-554 [PMID: 16998363 DOI: 10.1097/01.sla.0000239005.26353.49]
- 31 Lee JC, Rogers FB, Horst MA. Application of a trauma

- intensivist model to a Level II community hospital trauma program improves intensive care unit throughput. *J Trauma* 2010; **69**: 1147-1152; discussion 1152-1153 [PMID: 21068618 DOI: 10.1097/TA.0b013e3181f5a867]
- 32 **Park CA**, McGwin G, Smith DR, May AK, Melton SM, Taylor AJ, Rue LW. Trauma-specific intensive care units can be cost effective and contribute to reduced hospital length of stay. *Am Surg* 2001; **67**: 665-670 [PMID: 11450785]
- 33 **Nathens AB**, Maier RV, Jurkovich GJ, Monary D, Rivara FP, Mackenzie EJ. The delivery of critical care services in US trauma centers: is the standard being met? *J Trauma* 2006; **60**: 773-783; discussion 783-784 [PMID: 16612297]
- 34 Medscape. Available from: URL: <http://emedicine.medscape.com/>
- 35 American College of Surgeons. National Trauma Databank. Accessed November 2002. Available from: URL: <https://www.facs.org/quality/programs/trauma/ntdb>
- 36 **Duane TM**, Rao IR, Aboutanos MB, Wolfe LG, Malhotra AK. Are trauma patients better off in a trauma ICU? *J Emerg Trauma Shock* 2008; **1**: 74-77 [PMID: 19561984 DOI: 10.4103/0974-2700.43183]
- 37 **American College of Surgeons Committee on Trauma**. Resources for optimal care of the injured patient 1999. Chicago: American College of Surgeons, 1998
- 38 **Shere-Wolfe RF**, Galvagno SM, Grissom TE. Critical care considerations in the management of the trauma patient following initial resuscitation. *Scand J Trauma Resusc Emerg Med* 2012; **20**: 68 [PMID: 22989116 DOI: 10.1186/1757-7241-20-68]
- 39 **Deitch EA**, Dayal SD. Intensive care unit management of the trauma patient. *Crit Care Med* 2006; **34**: 2294-2301 [PMID: 16878037 DOI: 10.1097/01.CCM.0000233857.94604.73]
- 40 **Mullick P**, Talwar V, Pawar M. Factors influencing morbidity in ICU trauma admissions – A 3 year retrospective analysis. *Indian J Anaesth* 2004; **48**: 111-115
- 41 **Stillwell M**, Caplan ES. The septic multiple-trauma patient. *Crit Care Clin* 1988; **4**: 345-373 [PMID: 3048591]
- 42 **Morgan AS**. Risk factors for infection in the trauma patient. *J Natl Med Assoc* 1992; **84**: 1019-1023 [PMID: 1296993]
- 43 **O'Mahony JB**, Palder SB, Wood JJ, McIrvine A, Rodrick ML, Demling RH, Mannick JA. Depression of cellular immunity after multiple trauma in the absence of sepsis. *J Trauma* 1984; **24**: 869-875 [PMID: 6238173]
- 44 **Hietbrink F**, Koenderman L, Rijkers G, Leenen L. Trauma: the role of the innate immune system. *World J Emerg Surg* 2006; **1**: 15 [PMID: 16759367]
- 45 **Hietbrink F**, Koenderman L, Althuisen M, Pillay J, Kamp V, Leenen LP. Kinetics of the innate immune response after trauma: implications for the development of late onset sepsis. *Shock* 2013; **40**: 21-27 [PMID: 23603769 DOI: 10.1097/SHK.0b013e318295a40a]
- 46 **Timmers TK**, Hulstaert PF, Leenen LP. Patient outcomes can be associated with organizational changes: a quality improvement case study. *Crit Care Nurs Q* 2000; **37**: 125-134 [PMID: 24309466 DOI: 10.1097/CNQ.0000000000000011]

P- Reviewer: Gurjar M, Juneja D, Vugt A **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Wu HL



Severe scrub typhus infection: Clinical features, diagnostic challenges and management

John Victor Peter, Thomas I Sudarsan, John Anthony J Prakash, George M Varghese

John Victor Peter, Thomas I Sudarsan, Medical Intensive Care Unit, Christian Medical College, Vellore 632004, Tamil Nadu, India

John Anthony J Prakash, Department of Microbiology, Christian Medical College, Vellore 632004, Tamil Nadu, India

George M Varghese, Department of Infectious Diseases, Christian Medical College, Vellore 632004, Tamil Nadu, India

Author contributions: Peter JV contributed to the study concept; Peter JV, Sudarsan TI, Prakash JAJ and Varghese GM searched the literature and obtained the relevant articles; Peter JV, Sudarsan TI, Prakash JAJ and Varghese GM wrote the article; Peter JV, Sudarsan TI, Prakash JAJ and Varghese GM approved the final manuscript for publication.

Conflict-of-interest statement: There is no conflict of interest or financial disclosure for all the authors.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. John Victor Peter, Professor, Head, Medical Intensive Care Unit, Christian Medical College, Vellore 632004, Tamil Nadu, India. peterjohnvictor@yahoo.com.au
Telephone: +91-416-2282693
Fax: +91-416-2202035

Received: November 6, 2014

Peer-review started: November 8, 2014

First decision: January 8, 2015

Revised: January 27, 2015

Accepted: April 8, 2015

Article in press: April 9, 2015

Published online: August 4, 2015

Abstract

Scrub typhus infection is an important cause of acute undifferentiated fever in South East Asia. The clinical picture is characterized by sudden onset fever with chills and non-specific symptoms that include headache, myalgia, sweating and vomiting. The presence of an eschar, in about half the patients with proven scrub typhus infection and usually seen in the axilla, groin or inguinal region, is characteristic of scrub typhus. Common laboratory findings are elevated liver transaminases, thrombocytopenia and leukocytosis. About a third of patients admitted to hospital with scrub typhus infection have evidence of organ dysfunction that may include respiratory failure, circulatory shock, mild renal or hepatic dysfunction, central nervous system involvement or hematological abnormalities. Since the symptoms and signs are non-specific and resemble other tropical infections like malaria, enteric fever, dengue or leptospirosis, appropriate laboratory tests are necessary to confirm diagnosis. Serological assays are the mainstay of diagnosis as they are easy to perform; the reference test is the indirect immunofluorescence assay (IFA) for the detection of IgM antibodies. However in clinical practice, the enzyme-linked immuno-sorbent assay is done due to the ease of performing this test and a good sensitivity and sensitivity when compared with the IFA. Paired samples, obtained at least two weeks apart, demonstrating a ≥ 4 fold rise in titre, is necessary for confirmation of serologic diagnosis. The mainstay of treatment is the tetracycline group of antibiotics or chloramphenicol although macrolides are used alternatively. In mild cases, recovery is complete. In severe cases with multi-organ failure, mortality may be as high as 24%.

Key words: Rickettsia; Diagnosis; Management; Outcome; Multi-organ failure

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Scrub typhus is an important differential diagnosis in patients who present with acute undifferentiated fever in South East Asia. Since the presentation may be non-specific, with features of organ failure in those with severe infection, early diagnosis and appropriate management is crucial. The presence of an eschar suggests scrub typhus infection. The diagnosis may be confirmed on serological assays, the reference test being the indirect immunofluorescence test for the detection of IgM antibodies. In those with mild infection, fever defervescence occurs in about 2-d with Doxycycline therapy.

Peter JV, Sudarsan TI, Prakash JAJ, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. *World J Crit Care Med* 2015; 4(3): 244-250 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/244.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.244>

INTRODUCTION

Scrub typhus infection is an important aetiology of acute undifferentiated fever in south-east Asia and India^[1,2]. It is a zoonotic rickettsial illness caused by *Orientia tsutsugamushi* and is endemic in the "Tsutsugamushi triangle" that extends from northern Japan and far eastern Russia to northern Australia in the south and Pakistan in the west^[3]. The reservoirs for infection are the chiggers (larva of trombiculid mite) and rats and humans are accidentally infected. It is transmitted by trombiculid mites in long grasses and in dirt-floor homes, with infection characterized by a flu-like illness of fever, headache and myalgia lasting approximately one week. In some, the illness progresses to multi-organ dysfunction syndrome and death.

DISTRIBUTION OF DISEASE

Scrub typhus is seen in several parts of South-East Asia including India^[4-11], Bangladesh^[12], China^[13], Taiwan^[14], South Korea^[15], Japan^[16] and Northern Australia^[17]. Although scrub typhus has been reported from isolated parts of these countries^[2,5,9,13,14], it is likely that this disease is ubiquitous. The majority of cases are from the rural areas given that these mites thrive in those environments. However acute infection as well as serological evidence of infection has been published from metropolitan cities^[10,11,13]. Outbreaks generally occur during the cooler months of the year after monsoons^[12].

In the endemic Asia-Pacific region, one billion people are estimated to be at risk of infection and one million cases of scrub typhus occur every year^[18]. The disease is responsible for nearly 1/4th of the febrile episodes in endemic areas^[19]. Mortality in severe case or with improper treatment may be as high as 30%^[20,21].

PATHOPHYSIOLOGY

The pathophysiological hallmark of scrub typhus is disseminated vasculitis^[22] with subsequent vascular injury that involves organs such as skin, liver, brain, kidney, meninges and the lung. The organism multiplies at the site of inoculation that progresses on to necrosis and evolves into an eschar with regional lymphadenopathy^[22]. Within a few days, patients develop rickettsemia with infection of the vascular endothelium resulting in vascular injury in several organs. The injury causes disseminated intravascular coagulation (DIC) with platelet consumption, vascular leak, pulmonary edema, shock, hepatic dysfunction and meningoencephalitis^[23-26].

MOLECULAR CHARACTERISTICS

O. tsutsugamushi expresses a type-specific protein, the 56-kDa protein, which is unique and not expressed by other bacteria or Rickettsiae. Since this protein sequence is unique, and contains cross-reacting epitopes, variations in this have resulted in the genetic diversity of *O. tsutsugamushi*^[27]. This protein has also been explored in the development of vaccines^[28]. Commonly reported strains include the prototype Karp strain and closely related strains (Karp-like strains), which are most frequent in endemic areas, as well as Gilliam, Kato, Kawasaki, TA763 and others^[28,29].

CLINICAL FEATURES

Scrub typhus presents as an acute undifferentiated fever. The incubation period for symptoms is between six and twenty-one days from exposure^[30]. The clinical picture is characterized by sudden onset fever with chills, headache, backache and myalgia, profuse sweating, vomiting and enlarged lymph nodes^[30]. In some patients, an eschar may develop at the site of chigger feeding, usually at sites where the skin surfaces meet, such as axilla, groin and inguinal areas^[31]. Although the eschar is reported to be less frequently observed in South Asian patients than in East Asian or Caucasians^[31], 55% of patients had an eschar in a recent study from South India^[27]. In a large retrospective analysis of 418 patients with confirmed scrub typhus and an eschar, a significant difference in the distribution of eschar was noted between males and females^[32]. In females it was primarily present in the chest and abdomen (42.3%), while in males it was present in the axilla, groin and genitalia (55.8%). Unusual sites of eschar were reported to be in the cheek, ear lobe and dorsum of the feet^[32].

Five to eight days after the onset of fever, a macular or maculopapular rash may appear on the trunk and later extend to the arms and the legs in a small proportion of patients^[31]. Complications of scrub typhus infection include pneumonia^[33], acute respiratory distress syndrome (ARDS) like picture^[34,35],

myocarditis^[36], encephalitis^[37], hepatitis^[38], DIC^[39], hemophagocytic syndrome^[40], acute kidney injury^[41], acute pancreatitis^[42], transient adrenal insufficiency^[43], subacute painful thyroiditis^[44] and presentation as an acute abdomen^[45].

Several neurological manifestations have been observed in the setting of scrub typhus infection. The most common neurological presentation in scrub typhus is as meningitis, meningoencephalitis or encephalitis^[46]. Others include cerebral venous thrombosis^[47], Guillain-Barre Syndrome^[48], transient Parkinsonism and myoclonus^[49], opsoclonus^[50], cerebellitis^[51], transverse myelitis^[52], polyneuropathy^[53], facial palsy^[54], abducens nerve palsy^[55] and bilateral optic neuritis^[56].

Multi-organ dysfunction is not uncommon in severe scrub typhus infection. In a recently published study of 116 patients admitted to an intensive care unit with severe scrub typhus infection, the admission Acute Physiology and Chronic Health Evaluation (APACHE) II score was 19.6 ± 8.2 ^[20]. Ninety-one patients in this cohort had dysfunction of 3 or more organs and 16 patients (15%) had evidence of dysfunction of all six organs. Respiratory dysfunction was predominant (96.6%) with ventilatory support required in 87.9%. Cardiovascular dysfunction was present in 61.7% and hepatic dysfunction in 63.8%. Thirteen patients (11.2%) were dialyzed. Hospital mortality in this ICU cohort was 24.1%^[20]. On logistic regression analysis, APACHE-II score and duration of fever were independently associated with mortality.

DIAGNOSIS

Acute febrile illness (AFI) may be categorized as differentiated fever, where there is an obvious focus of infection (*e.g.*, respiratory tract, urinary tract) or an undifferentiated fever. In an undifferentiated fever, where there is no obvious focus of infection and the symptoms and signs are quite nonspecific, several diagnostic possibilities are considered, particularly in the tropics^[2]. This includes scrub typhus, malaria, enteric fever, dengue, leptospirosis, spotted fever rickettsioses and Hanta virus^[2]. Thus, in this setting, it is particularly important that a detailed clinical history and examination are done and relevant diagnostic tests performed to diagnose the cause of AFI. The presence of an eschar makes the diagnosis of scrub typhus highly likely and this should be carefully looked for.

The diagnostic methods available for laboratory confirmation include identification of the organism in cell culture, detection of the antigen by immunohistochemical methods or the antibodies by the indirect immunofluorescence assay (IFA) and finding specific nucleic acid targets using molecular methods. The success of a test in confirming the diagnosis of scrub typhus is dependent on the type of sample taken^[57] and the timing of the specimen. Cell culture or molecular assays performed using eschar (when present) or buffy coat are more likely to be positive in the first two weeks

of illness^[58]. Antibody levels reach detectable levels by day seven; paired sera obtained at least two weeks apart are necessary for serologically confirming the diagnosis by demonstration of a ≥ 4 fold rise in titre^[59].

Isolation of *Orientia tsutsugamushi* in culture is definitive and can be performed using cell culture^[60]. Cell lines like HeLa cells, L929 cells (mouse fibroblast cells), Vero cells, BHK-21 cells have been used to cultivate *Orientia tsutsugamushi*. The L929 mouse fibroblast cell line is commonly used for the isolation of *O. tsutsugamushi* from the blood. Isolation of *Orientia tsutsugamushi* is not routinely done as it requires a cell culture facility, trained personnel, strict bio-safety precautions and a BSL (Bio Safety level) III facility. As the organism doubling time is 9-18 h^[61], it takes an average of four weeks for identification by culture^[57]. This further precludes the use of culture as a routine diagnostic test. Currently, reference laboratories use culture techniques for isolation of *Orientia tsutsugamushi* for definitive identification, research and for obtaining antigen for immunofluorescence^[62].

Since antigen detection tests have low sensitivity/specificity and require biopsy specimens, in the clinical setting, serological assays are the mainstay of diagnosis^[63] as they are simple and comparatively easy to perform^[64]. The serological reference test is the indirect IFA for the detection of IgM antibodies. This assay has drawbacks which include retrospective nature, requirement of well trained personnel and equipment which may not be available in many diagnostic laboratories^[65]. Currently most diagnostic laboratories use the enzyme-linked immunosorbent assay (ELISA) for the detection of IgM antibodies in scrub typhus as it provides an objective result and has sensitivity similar to that of IFA^[64]. Detection of IgM antibody is considered to be diagnostic of an acute infection when compared to IgG antibodies which suggest a previous infection especially in endemic areas^[66]. Rapid tests to detect IgM antibodies to scrub typhus have sensitivity ranging from 34.7% to 96.7% and specificity between 93.3% and 99.7%^[66-68].

PCR assays, either conventional or real-time, targeting the 56 kDa gene, 47 kDa gene, *16 S rRNA* and *groEL* gene have also been explored and reported to have specificity approaching 100%^[24]. Sensitivity of the nested PCR assays using 56 kDa or the *16 S rRNA* genes can be as low as 22.5% to 36.1%^[9]. Real-time PCR assays show a better sensitivity ranging from 45%^[69] to 82%^[70]. In recent times, LAMP assays targeting the *GroEl* and the 47 kDa gene have been described^[71,72]. The LAMP assay has the advantage that it can be performed using simpler equipment. In addition it is not inhibited by heme as is the case with PCR^[73].

In the clinical setting, a diagnosis of scrub typhus is considered when a patient with an AFI has an eschar and a positive IgM ELISA for scrub typhus and other causes of fever excluded^[74]. In the absence of an eschar, a positive IgM ELISA in the appropriate clinical setting with defervescence within 48-h of initiation of

Table 1 Commonly used antimicrobial agents in scrub typhus infection

Name of drug	Dose and administration in adults	Comments
Doxycycline ^[75,77]	100 mg twice daily for 7 d	Drug of choice Intravenous preferred for sicker patients Rapid defervescence within 48 h
Tetracycline ^[76]	500 mg four times daily	No difference between doxycycline and tetracycline
Azithromycin ^[75,77]	Mild infections: 500 mg single dose Severe infections: 500 mg once daily for 3 to 5 d; 1 g loading dose may be given	Preferred drug in pregnancy In mild cases symptom duration similar when compared with doxycycline Recommended when doxycycline resistance is present
Telithromycin ^[80]	800 mg daily for 5 d	As effective as doxycycline
Chloramphenicol ^[75,77]	500 mg every 6 h for 7 d	Most common alternative to tetracycline Contraindicated in pregnancy Risk of aplastic anemia
Rifampicin ^[78]	600 to 900 mg daily for 7 d	Combination with doxycycline not more efficacious than either Rifampicin or doxycycline in mild scrub typhus Shorter duration of fever with Rifampicin in Northern Thailand when compared with Doxycycline Caution in tuberculosis endemic areas

doxycycline or scrub IgM ELISA seroconversion on convalescent sera with other etiologies of AFI ruled out with appropriate investigations also suggests scrub typhus infection^[2].

TREATMENT

Supportive treatment

Patients with mild disease presenting with fever without organ dysfunction may require only antipyretics along with antibiotics. Patients presenting with organ dysfunction would need organ support depending on the nature and extent of organ dysfunction^[20]. Patients with respiratory failure could be supported either by means of non-invasive or invasive mechanical ventilation based on standard criteria in the management of respiratory failure. Those with circulatory shock can be treated with fluid resuscitation and vasoactive therapy if the blood pressure does not improve with fluids. Acute kidney injury, which is not uncommon in scrub typhus, may need renal replacement therapy. Those with DIC with clinical bleeding would require transfusion of blood products depending on the nature of coagulation derangement.

Specific treatment

The drug treatment options in scrub typhus have been evaluated and summarized in a recent meta-analysis^[75]. In the 17 studies that were included in the meta-analyses, six antibiotics were used and included doxycycline, chloramphenicol, azithromycin, rifampicin, roxithromycin and tetracycline. Conventionally, the treatment of scrub typhus involves the use of the tetracycline group of antibiotics^[76] or chloramphenicol^[75]. Since these drugs are contraindicated in pregnancy and in children, alternative agents such as quinolones and macrolides are used for the treatment of scrub typhus in this setting^[75].

In the four studies that compared azithromycin with chloramphenicol, chloramphenicol treatment was

associated with significantly shorter median time to clearance of fever and lower adverse events when compared with azithromycin^[75]. Six studies compared doxycycline with chloramphenicol; symptom clearance time was significantly shorter with doxycycline^[75]. No significant differences were observed in symptom duration comparing azithromycin with doxycycline (3 studies), roxithromycin with doxycycline (3 studies) and doxycycline with either rifampicin or tetracycline (2 studies each)^[75].

Doxycycline is the preferred drug in the treatment of scrub typhus. A therapeutic response to doxycycline therapy is used as a diagnostic test^[2]. In less sick patients oral doxycycline can be administered at 100 mg twice daily. The duration of treatment is 7 d. In critically ill patients, particularly those in shock, the absorption of enterally administered doxycycline may be problematic. In such situations, intravenous doxycycline should be used; where unavailable, intravenous azithromycin may be used in isolation or combined with enteral doxycycline^[20,74]. Azithromycin is also the recommended drug for treatment of scrub typhus in pregnancy^[77]. Rifampicin may be considered where doxycycline resistance is present^[77]. In one trial of patients with mild scrub typhus, Rifampicin was found to have shorter defervescence time when compared with doxycycline^[78]. However, in tuberculosis endemic countries, rifampicin should be avoided for the treatment of scrub typhus. Although there is some evidence for the use of quinolones in scrub typhus, recent reports of quinolone resistance suggests that this treatment should not be used in critically ill patients^[79]. Preliminary reports suggest that Telithromycin is a promising new antibacterial agent for patients with mild to moderate scrub typhus^[80]. The different anti-microbial agents used in scrub typhus are summarized in Table 1.

COURSE

Patients with mild disease usually recover fully. In a

study of 261 patients from Taiwan, no mortality was observed^[81]. In a recently published large cohort of 623 patients hospitalized with scrub typhus of varying illness severity from mild to critically ill, the mortality was 9%^[35]. Reducing mortality over a 4-year period was reported in this study. Favourable maternal and fetal outcome may be expected in appropriately managed patients with scrub typhus complicating pregnancy^[82]. In sicker patients admitted to the ICU with multi-organ failure, the mortality is 24%^[20]. These observations should encourage clinicians to approach scrub typhus infection with optimism.

REFERENCES

- 1 Silpapojakul K. Scrub typhus in the Western Pacific region. *Ann Acad Med Singapore* 1997; **26**: 794-800 [PMID: 9522982]
- 2 Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, Abraham AM, Abraham OC, Thomas K. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. *Trop Doct* 2010; **40**: 230-234 [PMID: 20870680 DOI: 10.1258/td.2010.100132]
- 3 Sharma P, Kakkar R, Kaore SN, Vadav VK, Sharma R. Geographical distribution, effect of season and life cycle of scrub typhus. *JK Science* 2010; **12**: 63-64
- 4 Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T. Scrub typhus meningitis in South India--a retrospective study. *PLoS One* 2013; **8**: e66595 [PMID: 23799119 DOI: 10.1371/journal.pone.0066595]
- 5 Ahmad S, Srivastava S, Verma SK, Puri P, Shirazi N. Scrub typhus in Uttarakhand, India: a common rickettsial disease in an uncommon geographical region. *Trop Doct* 2010; **40**: 188-190 [PMID: 20555054 DOI: 10.1258/td.2010.090447]
- 6 Chaudhry D, Garg A, Singh I, Tandon C, Saini R. Rickettsial diseases in Haryana: not an uncommon entity. *J Assoc Physicians India* 2009; **57**: 334-337 [PMID: 19702040]
- 7 Gurung S, Pradhan J, Bhutia PY. Outbreak of scrub typhus in the North East Himalayan region-Sikkim: an emerging threat. *Indian J Med Microbiol* 2013; **31**: 72-74 [PMID: 23508434 DOI: 10.4103/0255-0857.108729]
- 8 Dass R, Deka NM, Duwarah SG, Barman H, Hoque R, Mili D, Barthakur D. Characteristics of pediatric scrub typhus during an outbreak in the North Eastern region of India: peculiarities in clinical presentation, laboratory findings and complications. *Indian J Pediatr* 2011; **78**: 1365-1370 [PMID: 21630069 DOI: 10.1007/s12098-011-0470-5]
- 9 Rathi NB, Rathi AN, Goodman MH, Aghai ZH. Rickettsial diseases in central India: proposed clinical scoring system for early detection of spotted fever. *Indian Pediatr* 2011; **48**: 867-872 [PMID: 21555807 DOI: 10.1007/s13312-011-0141-7]
- 10 Narvencar KP, Rodrigues S, Nevrekar RP, Dias L, Dias A, Vaz M, Gomes E. Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa. *Indian J Med Res* 2012; **136**: 1020-1024 [PMID: 23391799]
- 11 Mittal V, Gupta N, Bhattacharya D, Kumar K, Ichhpurani RL, Singh S, Chhabra M, Rana UV. Serological evidence of rickettsial infections in Delhi. *Indian J Med Res* 2012; **135**: 538-541 [PMID: 22664504]
- 12 Maude RR, Maude RJ, Ghose A, Amin MR, Islam MB, Ali M, Bari MS, Majumder MI, Tanganuchitcharnchai A, Dondorp AM, Paris DH, Bailey RL, Faiz MA, Blacksell SD, Day NP. Serosurveillance of Orientia tsutsugamushi and Rickettsia typhi in Bangladesh. *Am J Trop Med Hyg* 2014; **91**: 580-583 [PMID: 25092819 DOI: 10.4269/ajtmh.13-0570]
- 13 Wei Y, Huang Y, Luo L, Xiao X, Liu L, Yang Z. Rapid increase of scrub typhus: an epidemiology and spatial-temporal cluster analysis in Guangzhou City, Southern China, 2006-2012. *PLoS One* 2014; **9**: e101976 [PMID: 25006820 DOI: 10.1371/journal.pone.0101976]
- 14 Lai CH, Chang LL, Lin JN, Tsai KH, Hung YC, Kuo LL, Lin HH, Chen YH. Human spotted fever group rickettsioses are underappreciated in southern Taiwan, particularly for the species closely-related to Rickettsia felis. *PLoS One* 2014; **9**: e95810 [PMID: 24755560 DOI: 10.1371/journal.pone.0095810]
- 15 Jin HS, Chu C, Han DY. Spatial distribution analysis of scrub typhus in Korea. *Osong Public Health Res Perspect* 2013; **4**: 4-15 [PMID: 24159523 DOI: 10.1016/j.phrp.2012.12.007]
- 16 Bang HA, Lee MJ, Lee WC. Comparative research on epidemiological aspects of tsutsugamushi disease (scrub typhus) between Korea and Japan. *Jpn J Infect Dis* 2008; **61**: 148-150 [PMID: 18362409]
- 17 Graves S, Stenos J. Rickettsioses in Australia. *Ann N Y Acad Sci* 2009; **1166**: 151-155 [PMID: 19538275 DOI: 10.1111/j.1749-6632.2009.04530.x]
- 18 Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis* 2003; **16**: 429-436 [PMID: 14501995 DOI: 10.1097/00001432-200310000-00009]
- 19 Chattopadhyay S, Richards AL. Scrub typhus vaccines: past history and recent developments. *Hum Vaccin* 2007; **3**: 73-80 [PMID: 17375000 DOI: 10.4161/hv.3.3.4009]
- 20 Griffith M, Peter JV, Karthik G, Ramakrishna K, Prakash JA, Kalki RC, Varghese GM, Chrispal A, Pichamuthu K, Iyyadurai R, Abraham OC. Profile of organ dysfunction and predictors of mortality in severe scrub typhus infection requiring intensive care admission. *Indian J Crit Care Med* 2014; **18**: 497-502 [PMID: 25136187 DOI: 10.4103/0972-5229.138145]
- 21 Sriwongpan P, Krittigamas P, Tantipong H, Patumanond J, Tawichasri C, Namwongprom S. Clinical risk-scoring algorithm to forecast scrub typhus severity. *Risk Manag Healthc Policy* 2013; **7**: 11-17 [PMID: 24379733 DOI: 10.2147/RMHP.S52470]
- 22 Dogra S. Recent advances in understanding pathophysiology of scrub typhus. *JK Science* 2010; **12**: 70-71
- 23 Settle EB, Pinkerton H, Corbett AJ. A pathologic study of tsutsugamushi disease (scrub typhus) with notes on clinico-pathologic correlation. *J Lab Clin Med* 1945; **30**: 639
- 24 Allen AC, Spitz S. A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and Other Rickettsial Diseases. *Am J Pathol* 1945; **21**: 603-681 [PMID: 19970829]
- 25 LEVINE HD. Pathologic study of thirty-one cases of scrub typhus fever with especial reference to the cardiovascular system. *Am Heart J* 1946; **31**: 314-328 [PMID: 21018737 DOI: 10.1016/0002-8703(46)90313-4]
- 26 Ewing EP, Takeuchi A, Shirai A, Osterman JV. Experimental infection of mouse peritoneal mesothelium with scrub typhus rickettsiae: an ultrastructural study. *Infect Immun* 1978; **19**: 1068-1075 [PMID: 417027]
- 27 Varghese GM, Janardhanan J, Trowbridge P, Peter JV, Prakash JA, Sathyendra S, Thomas K, David TS, Kavitha ML, Abraham OC, Mathai D. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. *Int J Infect Dis* 2013; **17**: e981-e987 [PMID: 23891643 DOI: 10.1016/j.ijid.2013.05.017]
- 28 Kelly DJ, Fuerst PA, Ching WM, Richards AL. Scrub typhus: the geographic distribution of phenotypic and genotypic variants of Orientia tsutsugamushi. *Clin Infect Dis* 2009; **48** Suppl 3: S203-S230 [PMID: 19220144]
- 29 Jiang J, Paris DH, Blacksell SD, Aukkanit N, Newton PN, Phetsouvanh R, Izzard L, Stenos J, Graves SR, Day NP, Richards AL. Diversity of the 47-kD HtrA nucleic acid and translated amino acid sequences from 17 recent human isolates of Orientia. *Vector Borne Zoonotic Dis* 2013; **13**: 367-375 [PMID: 23590326 DOI: 10.1089/vbz.2012.1112]
- 30 Devine J. A review of scrub typhus management in 2000-2001 and implications for soldiers. *Journal of Rural Remote Environmental Health* 2003; **1**: 14-20
- 31 Jeong YJ, Kim S, Wook YD, Lee JW, Kim KI, Lee SH. Scrub typhus: clinical, pathologic, and imaging findings. *Radiographics* 2007; **27**: 161-172 [PMID: 17235005 DOI: 10.1148/rg.271065074]

- 32 **Kundavaram AP**, Jonathan AJ, Nathaniel SD, Varghese GM. Eschar in scrub typhus: a valuable clue to the diagnosis. *J Postgrad Med* 2013; **59**: 177-178 [PMID: 24029193 DOI: 10.4103/0022-3859.118033]
- 33 **Im JH**, Baek JH, Lee JS, Chung MH, Lee SM, Kang JS. A case series of possibly recrudescent *Orientia tsutsugamushi* infection presenting as pneumonia. *Jpn J Infect Dis* 2014; **67**: 122-126 [PMID: 24647257]
- 34 **Saxena A**, Khiangte B, Tiewsoh I. Scrub typhus complicated by acute respiratory distress syndrome and multiorgan failure; an unrecognized alarming entity in central India: a report of two cases. *J Family Med Prim Care* 2014; **3**: 80-83 [PMID: 24791245 DOI: 10.4103/2249-4863.130334]
- 35 **Varghese GM**, Trowbridge P, Janardhanan J, Thomas K, Peter JV, Mathews P, Abraham OC, Kavitha ML. Clinical profile and improving mortality trend of scrub typhus in South India. *Int J Infect Dis* 2014; **23**: 39-43 [PMID: 24661931 DOI: 10.1016/j.ijid.2014.02.009]
- 36 **Sittiwangkul R**, Pongprot Y, Silviliarat S, Oberdorfer P, Jittamala P, Sirisanthana V. Acute fulminant myocarditis in scrub typhus. *Ann Trop Paediatr* 2008; **28**: 149-154 [PMID: 18510826 DOI: 10.1179/146532808X302189]
- 37 **Kar A**, Dhanaraj M, Dedeepiya D, Harikrishna K. Acute encephalitis syndrome following scrub typhus infection. *Indian J Crit Care Med* 2014; **18**: 453-455 [PMID: 25097358 DOI: 10.4103/0972-5229.136074]
- 38 **Chung JH**, Lim SC, Yun NR, Shin SH, Kim CM, Kim DM. Scrub typhus hepatitis confirmed by immunohistochemical staining. *World J Gastroenterol* 2012; **18**: 5138-5141 [PMID: 23049227 DOI: 10.3748/wjg.v18.i36.5138]
- 39 **Ono Y**, Ikegami Y, Tasaki K, Abe M, Tase C. Case of scrub typhus complicated by severe disseminated intravascular coagulation and death. *Emerg Med Australas* 2012; **24**: 577-580 [PMID: 23039302 DOI: 10.1111/j.1742-6723.2012.01600.x]
- 40 **Lin YH**, Lin YH, Shi ZY. A case report of scrub typhus-associated hemophagocytic syndrome and a review of literature. *Jpn J Infect Dis* 2014; **67**: 115-117 [PMID: 24647254 DOI: 10.7883/yoken.67.115]
- 41 **Vikrant S**, Dheer SK, Parashar A, Gupta D, Thakur S, Sharma A, Kaushal SS, Kanga A. Scrub typhus associated acute kidney injury - a study from a tertiary care hospital from western Himalayan State of India. *Ren Fail* 2013; **35**: 1338-1343 [PMID: 23952649 DOI: 10.3109/0886022X.2013.828257]
- 42 **Bhatt A**, Menon AA, Bhat R, Gurusiddana SG. Pancreatitis in scrub typhus. *J Glob Infect Dis* 2014; **6**: 28-30 [PMID: 24741228 DOI: 10.4103/0974-777X.127947]
- 43 **Mookkappan S**, Basheer A, Chidambaram S, Natarajan N, Shrimanth B. Transient adrenal insufficiency and post-treatment bradycardia in scrub typhus - a case report. *Australas Med J* 2014; **7**: 164-167 [PMID: 24719653 DOI: 10.4066/AMJ.2014.1951]
- 44 **Mahajan SK**, Babu SN, Sharma D, Singh D, Kanga A, Kaushal SS. Scrub typhus presenting as acute abdomen. *Trop Doct* 2011; **41**: 185-186 [PMID: 21724691 DOI: 10.1258/td.2011.110079]
- 45 **Kim Sh**, Park TS, Baek HS, Jin HY. Subacute painful thyroiditis accompanied by scrub typhus infection. *Endocrine* 2013; **44**: 546-548 [PMID: 23564597 DOI: 10.1007/s12020-013-9947-5]
- 46 **Misra UK**, Kalita J, Mani VE. Neurological manifestations of scrub typhus. *J Neurol Neurosurg Psychiatry* 2015; **86**: 761-766 [PMID: 25209416 DOI: 10.1136/jnnp-2014-308722]
- 47 **Jena SS**, Mathew A, Sanjith A, Ajith S, Nair BR, Prakash J. Cerebral venous sinus thrombosis presentation in severe scrub typhus infection: a rare entity. *Neurol India* 2014; **62**: 308-310 [PMID: 25033856 DOI: 10.4103/0028-3886.136991]
- 48 **Sawale VM**, Upreti S, Singh TS, Singh NB, Singh TB. A rare case of Guillain-Barre syndrome following scrub typhus. *Neurol India* 2014; **62**: 82-83 [PMID: 24608469 DOI: 10.4103/0028-3886.128340]
- 49 **Chiou YH**, Yang CJ, Lai TH. Scrub typhus associated with transient parkinsonism and myoclonus. *J Clin Neurosci* 2013; **20**: 182-183 [PMID: 23010430 DOI: 10.1016/j.jocn.2012.01.047]
- 50 **D'sa S**, Singh S, Sowmya S. Opsoclonus in scrub typhus. *J Postgrad Med* 2012; **58**: 296-297 [PMID: 23298927 DOI: 10.4103/0022-3859.105453]
- 51 **Karanth SS**, Gupta A, Prabhu M. Pure cerebellitis due to scrub typhus: a unique case report. *Trop Doct* 2013; **43**: 41-42 [PMID: 23550204 DOI: 10.1177/0049475513480775]
- 52 **Lee KL**, Lee JK, Yim YM, Lim OK, Bae KH. Acute transverse myelitis associated with scrub typhus: case report and a review of literatures. *Diagn Microbiol Infect Dis* 2008; **60**: 237-239 [PMID: 17997258 DOI: 10.1016/j.diagmicrobio.2007.09.015]
- 53 **Kim JH**, Lee SA, Ahn TB, Yoon SS, Park KC, Chang DI, Chung KC. Polyneuropathy and cerebral infarction complicating scrub typhus. *J Clin Neurol* 2008; **4**: 36-39 [PMID: 19513323 DOI: 10.3988/jcn.2008.4.1.36]
- 54 **Lin WR**, Chen TC, Lin CY, Lu PL, Chen YH. Bilateral simultaneous facial palsy following scrub typhus meningitis: a case report and literature review. *Kaohsiung J Med Sci* 2011; **27**: 573-576 [PMID: 22208541 DOI: 10.1016/j.kjms.2011.10.003]
- 55 **Bhardwaj B**, Panda P, Revannasiddaiah S, Bhardwaj H. Abducens nerve palsy in a patient with scrub typhus: a case report. *Trop Biomed* 2013; **30**: 706-709 [PMID: 24522141]
- 56 **Cho HJ**, Choi JH, Sung SM, Jung DS, Choi KD. Bilateral optic neuritis associated with scrub typhus. *Eur J Neurol* 2013; **20**: e129-e130 [PMID: 24433476 DOI: 10.1111/ene.12268]
- 57 **Koh GC**, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. *Am J Trop Med Hyg* 2010; **82**: 368-370 [PMID: 20207857 DOI: 10.4269/ajtmh.2010.09-0233]
- 58 **Richards AL**. Worldwide detection and identification of new and old rickettsiae and rickettsial diseases. *FEMS Immunol Med Microbiol* 2012; **64**: 107-110 [PMID: 22067055 DOI: 10.1111/j.1574-695X.2011.00875.x]
- 59 **Cowan GD**, Friman G, Gunther G. Rickettsial Infections. In: Cook GC, Zumla AI, editors. *Manson's Tropical Diseases*. London: Saunders, 2009: 885-902
- 60 **Jiang J**, Chan TC, Temenak JJ, Dasch GA, Ching WM, Richards AL. Development of a quantitative real-time polymerase chain reaction assay specific for *Orientia tsutsugamushi*. *Am J Trop Med Hyg* 2004; **70**: 351-356 [PMID: 15100446]
- 61 **Tamura A**, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a new genus, *Orientia* gen. nov., as *Orientia tsutsugamushi* comb. nov. *Int J Syst Bacteriol* 1995; **45**: 589-591 [PMID: 8590688 DOI: 10.1099/00207713-45-3-589]
- 62 **Ching WM**, Wang H, Eamsila C, Kelly DJ, Dasch GA. Expression and refolding of truncated recombinant major outer membrane protein antigen (r56) of *Orientia tsutsugamushi* and its use in enzyme-linked immunosorbent assays. *Clin Diagn Lab Immunol* 1998; **5**: 519-526 [PMID: 9665960]
- 63 **Saisongkroh W**, Chenchittikul M, Silpapojakul K. Evaluation of nested PCR for the diagnosis of scrub typhus among patients with acute pyrexia of unknown origin. *Trans R Soc Trop Med Hyg* 2004; **98**: 360-366 [PMID: 15099992 DOI: 10.1016/j.trstmh.2003.10.012]
- 64 **McDade JE**. Rickettsial diseases. In: Hausler WK, Sussman M, editors. *Topley & Wilson's Microbiology & Microbial Infections*. London: Arnold, 1998: 995-1011
- 65 **Paris DH**, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. *Am J Trop Med Hyg* 2013; **89**: 301-307 [PMID: 23926142 DOI: 10.4269/ajtmh.13-0064]
- 66 **Blacksell SD**, Jenjaroen K, Phetsouvanh R, Wuthiekanun V, Day NP, Newton PN, Ching WM. Accuracy of AccessBio Immunoglobulin M and Total Antibody Rapid Immunochromatographic Assays for the Diagnosis of Acute Scrub Typhus Infection. *Clin Vaccine Immunol* 2010; **17**: 263-266 [PMID: 20016046 DOI: 10.1128/CVI.00448-08]
- 67 **Blacksell SD**, Jenjaroen K, Phetsouvanh R, Tanganuchitcharnchai A, Phouminh P, Phongmany S, Day NP, Newton PN. Accuracy of rapid IgM-based immunochromatographic and immunoblot assays for diagnosis of acute scrub typhus and murine typhus infections in Laos. *Am J Trop Med Hyg* 2010; **83**: 365-369 [PMID: 20682883 DOI: 10.4269/ajtmh.2010.09-0534]
- 68 **Blacksell SD**, Paris DH, Chierakul W, Wuthiekanun V, Teeratakul A, Kantipong P, Day NP. Prospective evaluation of commercial

- antibody-based rapid tests in combination with a loop-mediated isothermal amplification PCR assay for detection of *Orientia tsutsugamushi* during the acute phase of scrub typhus infection. *Clin Vaccine Immunol* 2012; **19**: 391-395 [PMID: 22219313 DOI: 10.1128/CVI.05478-11]
- 69 **Paris DH**, Blacksell SD, Newton PN, Day NP. Simple, rapid and sensitive detection of *Orientia tsutsugamushi* by loop-isothermal DNA amplification. *Trans R Soc Trop Med Hyg* 2008; **102**: 1239-1246 [PMID: 18565558 DOI: 10.1016/j.trstmh.2008.04.040]
- 70 **Kim DM**, Park G, Kim HS, Lee JY, Neupane GP, Graves S, Stenos J. Comparison of conventional, nested, and real-time quantitative PCR for diagnosis of scrub typhus. *J Clin Microbiol* 2011; **49**: 607-612 [PMID: 21068287 DOI: 10.1128/JCM.01216-09]
- 71 **Paris DH**, Blacksell SD, Nawtaisong P, Jenjaroen K, Teeraratkul A, Chierakul W, Wuthiekanun V, Kantipong P, Day NP. Diagnostic accuracy of a loop-mediated isothermal PCR assay for detection of *Orientia tsutsugamushi* during acute Scrub Typhus infection. *PLoS Negl Trop Dis* 2011; **5**: e1307 [PMID: 21931873 DOI: 10.1371/journal.pntd.0001307]
- 72 **Huber E**, Ji D, Howell L, Zhang Z, Chen HW, Ching WM, Chao CC. Loop-mediated isothermal amplification assay targeting the 47-kDa gene of *Orientia tsutsugamushi*: a rapid and sensitive alternative to real-time PCR. *J Med Microb Diagn* 2012; **1**: 112 [DOI: 10.4172/2161-0703.1000112]
- 73 **Notomi T**, Okayama H, Masubuchi H, Yonekawa T, Watanabe K, Amino N, Hase T. Loop-mediated isothermal amplification of DNA. *Nucleic Acids Res* 2000; **28**: E63 [PMID: 10871386 DOI: 10.1093/nar/28.12.e63]
- 74 **Peter JV**, Karthik G, Ramakrishna K, Griffith MF, Jude Prakash JA, Job V, Chacko B, Graham PL. Elevated procalcitonin is associated with increased mortality in patients with scrub typhus infection needing intensive care admission. *Indian J Crit Care Med* 2013; **17**: 174-177 [PMID: 24082615 DOI: 10.4103/0972-5229.117063]
- 75 **Fang Y**, Huang Z, Tu C, Zhang L, Ye D, Zhu BP. Meta-analysis of drug treatment for scrub typhus in Asia. *Intern Med* 2012; **51**: 2313-2320 [PMID: 22975540 DOI: 10.2169/intermedicine.51.7816]
- 76 **Song JH**, Lee C, Chang WH, Choi SW, Choi JE, Kim YS, Cho SR, Ryu J, Pai CH. Short-course doxycycline treatment versus conventional tetracycline therapy for scrub typhus: a multicenter randomized trial. *Clin Infect Dis* 1995; **21**: 506-510 [PMID: 8527534 DOI: 10.1093/clinids/21.3.506]
- 77 **Rajapakse S**, Rodrigo C, Fernando SD. Drug treatment of scrub typhus. *Trop Doct* 2011; **41**: 1-4 [PMID: 21172901 DOI: 10.1258/td.2010.100311]
- 78 **Watt G**, Kantipong P, Jongsakul K, Watcharapichat P, Phulsuksombati D, Strickman D. Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: a randomised trial. *Lancet* 2000; **356**: 1057-1061 [PMID: 11009140 DOI: 10.1016/S0140-6736(00)02728-8]
- 79 **Jang HC**, Choi SM, Jang MO, Ahn JH, Kim UJ, Kang SJ, Shin JH, Choy HE, Jung SI, Park KH. Inappropriateness of quinolone in scrub typhus treatment due to *gyrA* mutation in *Orientia tsutsugamushi* Boryong strain. *J Korean Med Sci* 2013; **28**: 667-671 [PMID: 23678256 DOI: 10.3346/jkms.2013.28.5.667]
- 80 **Kim DM**, Yu KD, Lee JH, Kim HK, Lee SH. Controlled trial of a 5-day course of telithromycin versus doxycycline for treatment of mild to moderate scrub typhus. *Antimicrob Agents Chemother* 2007; **51**: 2011-2015 [PMID: 17404000 DOI: 10.1128/AAC.01460-06]
- 81 **Su TH**, Liu CJ, Chen DS, Kao JH. Milder clinical manifestation of scrub typhus in Kinmen, Taiwan. *J Formos Med Assoc* 2013; **112**: 201-207 [PMID: 23537866 DOI: 10.1016/j.jfma.2012.02.002]
- 82 **Kim YS**, Lee HJ, Chang M, Son SK, Rhee YE, Shim SK. Scrub typhus during pregnancy and its treatment: a case series and review of the literature. *Am J Trop Med Hyg* 2006; **75**: 955-959 [PMID: 17123995]

P- Reviewer: Chen XL, Gurjar M **S- Editor:** Tian YL **L- Editor:** A
E- Editor: Wu HL



Clinical Trials Study

Landiolol, an ultra-short-acting β 1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis

Masaki Okajima, Masayuki Takamura, Takumi Taniguchi

Masaki Okajima, Takumi Taniguchi, Intensive Care Unit, Kanazawa University Hospital, Kanazawa 920-8641, Japan

Masayuki Takamura, Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medicine, Kanazawa 920-8641, Japan

Author contributions: Okajima M, Takamura M and Taniguchi T contributed to this manuscript.

Institutional review board statement: The study was reviewed and approved by the Kanazawa University Hospital Institutional Review Board.

Clinical trial registration: This study is registered at <http://www.controlled-trials.com/isrctn/>. The registration identification number is ISRCTN 70831305.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors state that they have no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at masaki46228@m-kanazawa.jp.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Masaki Okajima, MD, PhD, Intensive Care Unit, Kanazawa University Hospital, 13-1 Takaramachi, Kanazawa 920-8641, Japan. masaki46228@m-kanazawa.jp
Telephone: +81-76-2652000

Fax: +81-76-2344339

Received: August 22, 2014
Peer-review started: August 22, 2014
First decision: September 28, 2014
Revised: April 15, 2015
Accepted: April 27, 2015
Article in press: April 29, 2015
Published online: August 4, 2015

Abstract

AIM: To investigate whether landiolol, an ultra-short-acting β 1-antagonist, can safely and effectively control heart rate in septic patients with supraventricular tachyarrhythmias.

METHODS: We reviewed all patients with sepsis who admitted to our intensive care unit between January 2006 and December 2011. Sixty one septic patients suffered from supraventricular tachyarrhythmias (heart rate ≥ 120 bpm for > 1 h). Among 61 patients, 39 patients were treated with landiolol (landiolol group) and 22 patients were not treated with landiolol (control group). Arterial pressure, heart rate, cardiac rhythm, pulmonary arterial pressure and cardiac output (if a pulmonary arterial catheter was inserted) were compared between the 2 groups at 1, 8 and 24 h after the initiation of tachyarrhythmias.

RESULTS: Mean age and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were similar between the 2 groups. Paroxysmal atrial fibrillation/flutter (87%), paroxysmal atrial tachycardia (10%), and paroxysmal supraventricular tachycardia (3%) were observed. The initial landiolol dose administered was 6.3 ± 5.8 g/kg per minute. Rapid and substantial reduction of heart rate was observed in the landiolol group without any

deterioration of hemodynamics. Landiolol significantly reduced heart rate (from 145 ± 14 bpm to 90 ± 20 bpm) compared to the control group (from 136 ± 21 bpm to 109 ± 18 bpm, $P < 0.05$). The conversion to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point ($P < 0.01$ at 8 h; $P < 0.05$ at 1 and 24 h).

CONCLUSION: Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmias.

Key words: Landiolol; Supraventricular tachyarrhythmias; Sepsis; Rate control; Conversion to sinus rhythm

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The management of tachyarrhythmia is important but it is often difficult because of unstable hemodynamics in septic patients. Landiolol is an ultra-short-acting β_1 selective adrenoceptor antagonist. It exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other β blockers. In fact, landiolol significantly reduced heart rate without any deterioration of hemodynamics in this study. The most impressive finding is high conversion rate to sinus rhythm immediately after landiolol administration. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias. Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting β_1 -blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med* 2015; 4(3): 251-257 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/251.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.251>

INTRODUCTION

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The incidence of paroxysmal atrial fibrillation/flutter (PAF) has been reported to be 31% in critically ill patients with sepsis^[1]. Tachyarrhythmias have been identified as a major source of morbidity in critically ill patients^[2,3]. Therefore, controlling tachyarrhythmia should be important in such patients.

Measurements of serum catecholamine level and direct measurements of renal sympathetic nerve activity have revealed that severe infection activates the sympathetic nervous system^[4-9]. This activation may trigger supraventricular tachyarrhythmias in the presence of severe infection^[10]. Therefore, we believed

that β blockers can be used to control heart rate (HR) in patients with severe infection. However, it is difficult to use β blocker in patients with severe sepsis because of hemodynamic instability.

Landiolol (ONOACT; Ono Pharmaceutical, Osaka, Japan), a newly developed commercially available agent, is an ultra-short-acting β -adrenoceptor antagonist with a half-life of 4 min in healthy subjects. Landiolol also has high β_1 selectivity ($\beta_1/\beta_2 = 255$) and is 8 times more cardioselective than esmolol^[11-14]. Moreover, landiolol exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol in rabbits^[15,16]. In clinical situations, landiolol has been used to treat perioperative tachyarrhythmias in Japan. Landiolol reduced HR significantly without reducing blood pressure and stabilized hemodynamics in postsurgical patients^[11,17-20].

Considering these characteristics, landiolol could be valuable and suitable for managing tachyarrhythmias in patients with severe infection. Therefore, we investigated whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in patients with severe sepsis.

MATERIALS AND METHODS

Study design and patients selection

This historical cohort, single-center, interventional, and inter-subjective comparison study was approved by the Institutional Review Board of the Kanazawa University Hospital and was registered under ISRCTN number 70831305. Informed consent was obtained from all patients.

Medical records of all patients were screened and followed for sepsis with supraventricular tachyarrhythmia by a single intensivist in the intensive care unit (ICU) of the Kanazawa University Hospital from January 2006 to December 2011, were reviewed. Patients were included in this study if they met the following criteria: (1) systemic inflammatory response syndrome score ≥ 2 with infection; (2) ≥ 18 years of age; (3) supraventricular tachyarrhythmias with HR ≥ 120 bpm for >1 h; (4) no history of chronic supraventricular tachyarrhythmias; and (5) no supraventricular tachyarrhythmias at the time of ICU admission. Patients were divided into 2 groups: those treated with landiolol (landiolol group) and those not treated with landiolol (control group) to control HR of supraventricular tachyarrhythmias.

Measurements

Arterial pressure and HR were compared between the 2 groups at 1, 8, and 24 h after the initiation of tachyarrhythmia. We also investigated heart rhythm and the conversion to sinus rhythm. Pulmonary arterial pressure, central venous pressure (CVP), cardiac output, and cardiac index (CI) were measured if a pulmonary arterial catheter was inserted. Systemic vascular resistance index (SVRI) was calculated as follows: SVRI

Table 1 Patients' characteristics

	Landiolol	Control
<i>n</i>	39	22
Age, yr	70.7 ± 12.3	70.8 ± 12.5
Underlying disease		
Cardiovascular disease	16 (41.0%)	11 (50.0%)
Malignancy	11 (28.2%)	3 (13.6%)
Immunological disorder	3 (7.7%)	2 (9.1%)
Others	9 (23.1%)	6 (27.2%)
Infected site		
Respiratory tract	17 (43.6%)	14 (63.6%)
Intra-abdominal	13 (33.3%) ^a	2 (9.1%)
Blood	5 (12.8%)	0 (0%)
Skin/soft tissue	2 (5.1%)	0 (0%)
Urinary tract	1 (2.6%) ^a	4 (18.2%)
Others	1 (2.6%)	2 (9.1%)
APACHE II	22.8 ± 5.4	22.1 ± 7.7
SOFA	8.8 ± 4.0	9.1 ± 3.9

^a*P* < 0.05 *vs* control. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

(dyne·s/cm⁵ per square meter) = 80 (mean arterial pressure-CVP)/CI.

Endpoints

The primary endpoint was HR reduction of the supraventricular tachyarrhythmias without a decrease in arterial pressure. The secondary endpoint was the frequency of conversion to sinus rhythm.

Statistical analysis

Continuous variables are expressed as mean ± SD. Patient characteristics and hemodynamics of the 2 groups were compared using an independent *t* test for continuous variables and with either Fisher's exact test or a chi-square test for categorical variables. Differences of conversion rates were analyzed with Fisher's exact test or the chi-square test as appropriate. Other data were analyzed by repeated-measures analysis of variance. In all analyses, *P* < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Masayuki Takamura, PhD from Kanazawa University Graduate School of Medicine.

RESULTS

A total of 188 septic patients were admitted to the ICU in this period. Among them, 23 patients were excluded from analysis because of less than 18 years of age. Two patients were excluded because of atrial fibrillation at the time of ICU admission. Supraventricular tachyarrhythmias occurred in 61 patients (37.4%) in leaving 163 septic patients. Among 61 patients, 39 patients were treated with landiolol and 22 patients were not treated with landiolol.

Patient characteristics are indicated in Table 1. There were no significant differences between the 2 groups with respect to age, underlying disease, Acute Physiology and Chronic Health Evaluation II score and

Table 2 Hemodynamics

	Landiolol	Control
Heart rate, bpm	145 ± 14 ^a	136 ± 21
Systolic arterial pressure, mmHg	113 ± 34 ^a	137 ± 39
Diastolic arterial pressure, mmHg	60 ± 17	66 ± 13
Mean arterial pressure, mmHg	78 ± 21	86 ± 28
Diastolic pulmonary arterial pressure, mmHg	19 ± 6	20 ± 7
Cardiac output, L/min	3.9 ± 1.7	5.8 ± 1.5
Cardiac index, L/min per square meter	2.5 ± 1.1 ^a	4.0 ± 1.3
SVRI, dyne·s/m ⁵ per square meter	2068 ± 795	1615 ± 399
Arrhythmia		
Paroxysmal atrial fibrillation/flutter	34 (87%)	13 (60%)
Paroxysmal atrial tachycardia	4 (10%)	8 (36%)
Paroxysmal supraventricular tachycardia	1 (3%)	1 (5%)
Concomitant drugs to control arrhythmia		
Calcium-channel blocker	3 (8%)	5 (22%)
Other β blockers	0 (0%)	3 (14%)
Disopyramid phosphate	0 (0%)	1 (5%)
Amiodarone	0 (0%)	1 (5%)

^a*P* < 0.05 *vs* control. SVRI: Systemic vascular resistance index.

Sequential Organ Failure Assessment. Intra-abdominal infection was more (*P* < 0.05) and urinary tract infection was less (*P* < 0.05) in landiolol group than in control group. Respiratory tract infection was the most frequent disease in both groups.

Baseline hemodynamics are summarized in Table 2. Baseline HR was higher in the landiolol group. Systolic arterial pressure and CI were lower in the landiolol group. PAF was the most frequent observation in both groups. Calcium channel blockers and antiarrhythmic agents were used to control HR or cardiac rhythm in the control group.

The initial dose of landiolol was 6.3 ± 3.3 g/kg per minute. Landiolol significantly reduced HR from 145 ± 14 bpm to 119 ± 28 bpm (*P* < 0.01) without reducing arterial pressure at 1 h after the initiation of tachyarrhythmia (Figures 1 and 2). At that time, HR did not change significantly in the control group (from 136 ± 21 bpm to 135 ± 21 bpm) (Figure 1). The conversion rate to sinus rhythm was 25.6% in the landiolol group but 0% in the control group (Figure 1, *P* < 0.05).

After that, a substantial reduction in HR was observed in the landiolol group without any deterioration of hemodynamics. At 24 h after the initiation of tachyarrhythmia, landiolol reduced HR dramatically from 145 ± 14 bpm to 90 ± 20 bpm (Figure 1). A lesser degree of HR reduction was seen in the control group (from 136 ± 21 bpm to 109 ± 18 bpm) than in the landiolol group (Figure 1). The conversion from to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point (Figure 1, *P* < 0.01 at 8 h; *P* < 0.05 at 24 h).

Baseline diastolic pulmonary arterial pressures were similar between groups and did not change (Figure 3). In the landiolol group, baseline CI was lower and did not decrease compared to the control group (Figure 3).

Finally, the duration of landiolol administration was 80.7 ± 78.5 h and the significant bradycardia have

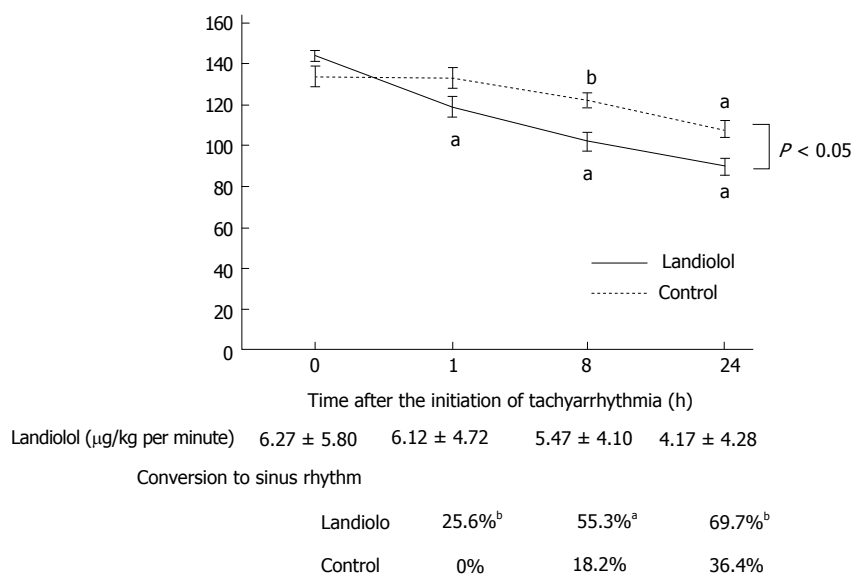


Figure 1 Heart rate and sinus rhythm conversion rate. Rapid and substantial reduction of heart rate (HR) was observed in the landiolol group. Reduction in HR was observed in the landiolol group than the control. In addition, the conversion from supraventricular arrhythmia to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point. Results are expressed as mean \pm SE. ^a $P < 0.01$, ^b $P < 0.05$ vs time 0 h.

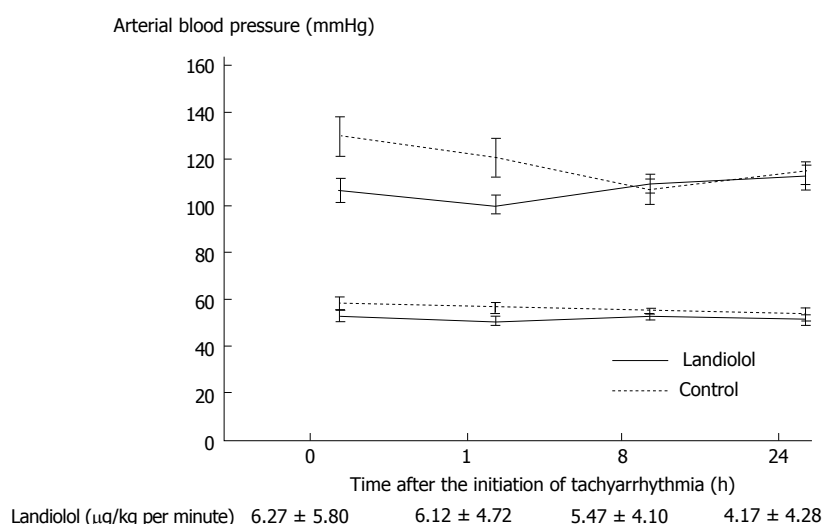


Figure 2 Arterial pressure. Landiolol did not change arterial blood pressure. Results are expressed as mean \pm SE.

never been observed in any treated patients.

DISCUSSION

This is the first report to investigate the clinical use of landiolol for treating supraventricular tachyarrhythmia in patients with severe sepsis. Its major findings are as follows: (1) low-dose landiolol rapidly and substantially reduced HR in septic patients with supraventricular tachyarrhythmia; (2) low-dose landiolol did not reduce arterial pressure and cardiac output; and (3) low-dose landiolol immediately and significantly converted supraventricular tachyarrhythmias to sinus rhythm in septic patients.

Severe infection or sepsis generally activates sympathetic nervous system. Plasma norepinephrine

and epinephrine plasma levels have been reported to be approximately 6 times and 60 times higher in conscious rats with endotoxemia than in control rats, respectively^[5]. In 1 human study, the serum levels of both norepinephrine and epinephrine were significantly higher in postoperative patients with sepsis than in those without sepsis^[4]. Moreover, by direct measurement of sympathetic nerve activity, renal sympathetic nerve activity was also increased approximately 3.5 fold by the systemic administration of lipopolysaccharide in rats^[6,21].

There is a close association between autonomic nervous system activity and supraventricular tachyarrhythmia. Sepsis-induced activation of the sympathetic nervous system is partially associated with supraventricular tachyarrhythmia in patients with severe sepsis^[10]. Sympathetic activation of the heart facilitates

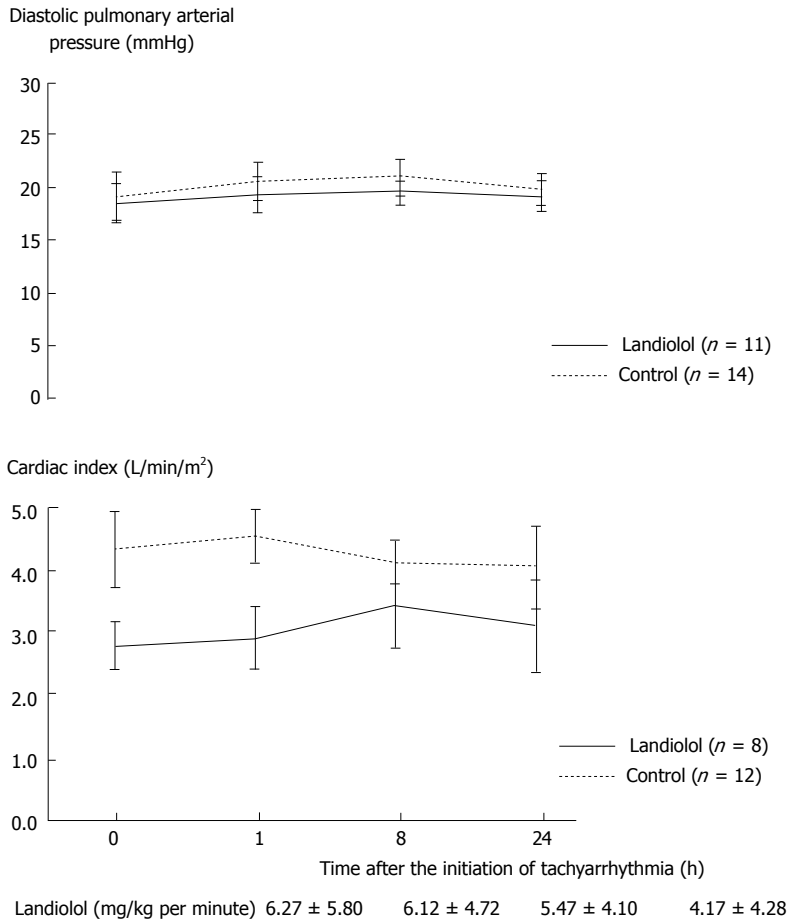


Figure 3 Pulmonary arterial catheter parameters. Landiolol did not affect diastolic pulmonary arterial pressure or cardiac index. Results are expressed as mean ± SE.

arrhythmogenesis by increasing calcium entry and the spontaneous release of calcium from the sarcoplasmic reticulum^[22,23]. Therefore, β blockers are the reasonable drug for controlling HR in the presence of supraventricular tachyarrhythmia in septic patients. The landiolol infusion at the dose of 5-10 μ g/kg per minute much lower than described dose in the package insert, significantly decreased HR in 82% of postoperative patients with PAF^[19]. Consistent with these previous studies, low-dose landiolol rapidly and substantially reduced HR in our septic patients with supraventricular tachyarrhythmia. Therefore, the low dose (6.3 ± 3.3 g/kg per minute) of landiolol administered was enough to inhibit excessive activation of sympathetic nerve activity and to significantly reduce HR in septic patients with tachyarrhythmia.

Landiolol reduced HR significantly without reducing arterial pressure and stabilized hemodynamics in postsurgical patients^[11,17-20]. Consistent with these studies, landiolol neither reduces arterial pressure nor deteriorates hemodynamics in our septic patients. Recent prospective, multicenter, single-blind, randomized, parallel-group study showed that low-dose landiolol rapidly decreased HR of atrial fibrillation/flutter without an increase in the incidence of adverse events in patients with LV dysfunction^[24]. Landiolol may have more negative chronotropic effect than negative inotropic effect, especially at a low dose. Landiolol has a higher β_1 -selectivity ($\beta_1/\beta_2 = 255$) and 8 times more

cardioselective than esmolol, which is also short-acting β_1 -selective β adrenergic receptor blocker^[11-14]. Landiolol exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol in rabbits^[15,16]. Consistent with these reports, in our study, landiolol did not decrease CI despite HR reduction. Another reason is that HR reduction by landiolol causes better hemodynamics. The landiolol-induced HR reduction in patients with tachyarrhythmia allows sufficient left ventricular filling time, which subsequently allows more stroke volume. Moreover, the conversion to sinus rhythm, in part, results in sufficient atrial kick, which also creates more stroke volume. Therefore, landiolol did not decrease arterial pressure and stabilized hemodynamics.

The most impressive findings in our study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. A few case studies have reported landiolol-induced conversion to sinus rhythm in patients with atrial fibrillation or flutter^[25,26]. Recently, landiolol has been reported to be more effective and safer than diltiazem for conversion to normal sinus rhythm in patients with postoperative atrial fibrillation after open heart surgery^[20]. Landiolol-induced reduction of HR improves hemodynamics and converts supraventricular tachyarrhythmias to

sinus rhythm. However, landiolol may function as an antiarrhythmic agent and directly affects the restoration to sinus rhythm. The use of β blockers has recently been reported to have an anti-oxidative and anti-inflammatory effect. However, no study has reported the antiarrhythmic effect of landiolol in supraventricular tachyarrhythmia. As the excessive sympathetic nervous activation caused by sepsis may be associated with maintaining supraventricular arrhythmia, landiolol that has more direct suppressive effect of sympathetic activity than other drugs may cause the conversion to sinus rhythm.

Our study has several potential limitations. First, as this is the historical cohort study, the drug selection for managing tachyarrhythmia was mainly dependent on intensivists or primary doctors examining the patient then. These selection biases might have affected the results observed. However landiolol was administered in more hemodynamically unstable patients, such as lower systolic blood pressure and lower CI, than control group. Therefore we believe that these selection biases may not overestimate the benefit of landiolol that we observed in results. Second, baseline arterial pressure was relatively high, and diastolic pulmonary arterial pressure was not very low. Because sufficient volume resuscitation was first conducted in our study, few patients with intravascular hypovolemia were observed. Third, the number of patients performed a pulmonary arterial catheter analysis was relatively a few in present study. Therefore, the power of the statistical analysis may be weak. However, we did not need to perform a pulmonary arterial catheter analysis because the patients' hemodynamics did not worsen. Therefore, we are convinced that landiolol did not cause hemodynamic deterioration. Finally, we did not evaluate prognosis such as ICU stay length or mortality. Although ICU stay length was similar between the 2 groups, mortality was higher in the control group than in the landiolol group. We did not perform multivariate analysis of mortality; therefore, this requires further investigation.

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing tachyarrhythmias in patients with sepsis.

ACKNOWLEDGMENTS

We thank patients and staff at Kanazawa University Hospital who participated in this project.

COMMENTS

Background

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The management of tachyarrhythmia is important as tachyarrhythmias have been identified as a major source of morbidity in critically ill patients. However it is often difficult because of unstable hemodynamics in septic patients.

Research frontiers

Landiolol, an ultra-short-acting β_1 selective adrenoceptor antagonist, exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other β blockers. The current research hotspots is whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in septic patients.

Innovations and breakthroughs

Landiolol significantly reduced heart rate without any deterioration of hemodynamics. The most impressive finding in the study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias.

Applications

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

Terminology

Landiolol, a newly developed commercially available agent, is an ultra-short-acting β -adrenoceptor antagonist (a half-life of 4 min), has high β_1 selectivity ($\beta_1/\beta_2 = 255$) and exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol.

Peer-review

The paper is interesting and well written.

REFERENCES

- 1 **Salman S**, Bajwa A, Gajic O, Afessa B. Paroxysmal atrial fibrillation in critically ill patients with sepsis. *J Intensive Care Med* 2008; **23**: 178-183 [PMID: 18443011 DOI: 10.1177/0885066608315838]
- 2 **Leibovici L**, Gaftor-Gvili A, Paul M, Almanasreh N, Tacconelli E, Andreassen S, Nielsen AD, Frank U, Cauda R. Relative tachycardia in patients with sepsis: an independent risk factor for mortality. *QJM* 2007; **100**: 629-634 [PMID: 17846061 DOI: 10.1093/qjmed/hcm074]
- 3 **Christian SA**, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. *J Crit Care* 2008; **23**: 532-536 [PMID: 19056018 DOI: 10.1016/j.jcrr.2007.09.005]
- 4 **Groves AC**, Griffiths J, Leung F, Meek RN. Plasma catecholamines in patients with serious postoperative infection. *Ann Surg* 1973; **178**: 102-107 [PMID: 4717703 DOI: 10.1097/0000658-197307000-00020]
- 5 **Jones SB**, Romano FD. Plasma catecholamines in the conscious rat during endotoxemia. *Circ Shock* 1984; **14**: 189-201 [PMID: 6391720]
- 6 **Cumming AD**, Kline R, Linton AL. Association between renal and sympathetic responses to nonhypotensive systemic sepsis. *Crit Care Med* 1988; **16**: 1132-1137 [PMID: 3168506 DOI: 10.1097/00003246-198811000-00010]
- 7 **Waddell SC**, Davison JS, Befus AD, Mathison RD. Role for the cervical sympathetic trunk in regulating anaphylactic and endotoxic shock. *J Manipulative Physiol Ther* 1992; **15**: 10-15 [PMID: 1740649]
- 8 **Saito M**, Akiyoshi M, Shimizu Y. Possible role of the sympathetic nervous system in responses to interleukin-1. *Brain Res Bull* 1991; **27**: 305-308 [PMID: 1959023 DOI: 10.1016/0361-9230(91)90116-2]
- 9 **Green PG**, Luo J, Heller PH, Levine JD. Further substantiation of a significant role for the sympathetic nervous system in inflammation.

- Neuroscience* 1993; **55**: 1037-1043 [PMID: 8232896 DOI: 10.1016/0306-4522(93)90317-9]
- 10 **Otake H**, Suzuki H, Honda T, Maruyama Y. Influences of autonomic nervous system on atrial arrhythmogenic substrates and the incidence of atrial fibrillation in diabetic heart. *Int Heart J* 2009; **50**: 627-641 [PMID: 19809211 DOI: 10.1536/ihj.50.627]
 - 11 **Atarashi H**, Kuruma A, Yashima M, Saitoh H, Ino T, Endoh Y, Hayakawa H. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000; **68**: 143-150 [PMID: 10976545 DOI: 10.1067/mcp.2000.108733]
 - 12 **Sugiyama A**, Takahara A, Hashimoto K. Electrophysiologic, cardiohemodynamic and beta-blocking actions of a new ultra-short-acting beta-blocker, ONO-1101, assessed by the in vivo canine model in comparison with esmolol. *J Cardiovasc Pharmacol* 1999; **34**: 70-77 [PMID: 10413070 DOI: 10.1097/00005344-199907000-00012]
 - 13 **Motomura S**, Hagihara A, Narumi Y, Hashimoto K. Time course of a new ultrashort-acting beta-adrenoceptor-blocking drug, ONO-1101: comparison with those of esmolol and propranolol by using the canine isolated, blood-perfused heart preparations. *J Cardiovasc Pharmacol* 1998; **31**: 431-440 [PMID: 9514189 DOI: 10.1097/00005344-199803000-00015]
 - 14 **Iguchi S**, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, Sakaki K, Hachiya K, Ichioka Y, Kawamura M. Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull (Tokyo)* 1992; **40**: 1462-1469 [PMID: 1356643 DOI: 10.1248/cpb.40.1462]
 - 15 **Sasao J**, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001; **48**: 985-989 [PMID: 11698317 DOI: 10.1007/BF03016588]
 - 16 **Ikeshita K**, Nishikawa K, Toriyama S, Yamashita T, Tani Y, Yamada T, Asada A. Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts. *J Anesth* 2008; **22**: 361-366 [PMID: 19011773 DOI: 10.1007/s00540-008-0640-4]
 - 17 **Konishi R**, Maeda R, Endo I, Inoue N, Seo N. Successful control of rapid heart rate in a patient with atrial fibrillation by continuous intravenous administration of landiolol hydrochloride. *Masui* 2003; **52**: 515-518 [PMID: 12795134]
 - 18 **Ogata J**, Okamoto T, Minami K. Landiolol for the treatment of tachyarrhythmia associated with atrial fibrillation. *Can J Anaesth* 2003; **50**: 753 [PMID: 12944459 DOI: 10.1007/BF03018726]
 - 19 **Yoshida Y**, Terajima K, Sato C, Akada S, Miyagi Y, Hongo T, Takeda S, Tanaka K, Sakamoto A. Clinical role and efficacy of landiolol in the intensive care unit. *J Anesth* 2008; **22**: 64-69 [PMID: 18306018 DOI: 10.1007/s00540-007-0573-3]
 - 20 **Sakamoto A**, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S. Landiolol, an ultra-short-acting β_1 -blocker, more effectively terminates atrial fibrillation than diltiazem after open heart surgery: prospective, multicenter, randomized, open-label study (JL-KNIGHT study). *Circ J* 2012; **76**: 1097-1101 [PMID: 22361918 DOI: 10.1253/circj.CJ-11-1332]
 - 21 **Pålsson J**, Ricksten SE, Delle M, Lundin S. Changes in renal sympathetic nerve activity during experimental septic and endotoxin shock in conscious rats. *Circ Shock* 1988; **24**: 133-141 [PMID: 3286033]
 - 22 **Bers DM**. Cardiac excitation-contraction coupling. *Nature* 2002; **415**: 198-205 [PMID: 11805843 DOI: 10.1038/415198a]
 - 23 **Ter Keurs HE**, Boyden PA. Calcium and arrhythmogenesis. *Physiol Rev* 2007; **87**: 457-506 [PMID: 17429038 DOI: 10.1152/physrev.00011.2006]
 - 24 **Nagai R**, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Aiba T, Kitakaze M, Sakamoto A, Ikeda T, Imai Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting β_1 -selective blocker landiolol with digoxin (J-Land Study). *Circ J* 2013; **77**: 908-916 [PMID: 23502991 DOI: 10.1253/circj.CJ-12-1618]
 - 25 **Matsumoto N**, Aomori T, Kanamoto M, Usui T, Shiga T, Yamamoto K, Saito S. Influence of hemodynamic variations on the pharmacokinetics of landiolol in patients undergoing cardiovascular surgery. *Biol Pharm Bull* 2012; **35**: 1655-1660 [PMID: 22864018 DOI: 10.1248/bpb.b110727]
 - 26 **Mayahara T**, Goto M, Sato M, Kanazawa T, Isomine S, Nakajima H, Sakaida K. Conversion of atrial fibrillation to sinus rhythm during landiolol infusion. *J Anesth* 2004; **18**: 304-306 [PMID: 15549475 DOI: 10.1007/s00540-004-0258-0]

P- Reviewer: Quesada A, Willms D, Yousef A **S- Editor:** Gong XM
L- Editor: A **E- Editor:** Wu HL



Observational Study

Outcomes of critically ill cancer patients with *Acinetobacter baumannii* infection

Silvio A Ñamendys-Silva, Paulina Correa-García, Francisco J García-Guillén, María O González-Herrera, Américo Pérez-Alonso, Julia Texcocano-Becerra, Angel Herrera-Gómez, Patricia Cornejo-Juárez, Abelardo Meneses-García

Silvio A Ñamendys-Silva, Francisco J García-Guillén, María O González-Herrera, Américo Pérez-Alonso, Julia Texcocano-Becerra, Angel Herrera-Gómez, Abelardo Meneses-García, Department of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico City 14080, Mexico

Silvio A Ñamendys-Silva, Department of Critical Care Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City 14000, Mexico

Paulina Correa-García, Division of Education and Research, Hospital de la Mujer, Mexico City 11340, Mexico

Patricia Cornejo-Juárez, Department of Infectious Diseases, Instituto Nacional de Cancerología, Mexico City 14080, Mexico

Author contributions: All authors contributed to this manuscript.

Institutional review board statement: This investigation was approved by the Scientific and Ethics Committees at INCAN, and the requirement for informed consent was waived (Rev/02/13). A copy of approval can be provided on request.

Informed consent statement: This study has been approved by the Bioethics Committee of INCAN, and the requirement for informed consent was waived.

Conflict-of-interest statement: None of the authors have commercial association or financial involvement that might pose a conflict of interest in connection with this article.

Data sharing statement: Data presented in the manuscript is anonymised and the risk of identifying individual patient is very low. No additional data is available other than stated in the manuscript for this study.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on

different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Silvio A Ñamendys-Silva, MD, MSc, FCCP, Department of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico. Av. San Fernando No. 22, Col. Sección XVI, Delegación Tlalpan, Mexico City 14080, Mexico. snamendys@incan.edu.mx
Telephone: +52-55-47471020

Received: February 12, 2015

Peer-review started: February 14, 2015

First decision: March 20, 2015

Revised: April 30, 2015

Accepted: May 16, 2015

Article in press: May 18, 2015

Published online: August 4, 2015

Abstract

AIM: To describe the intensive care unit (ICU) outcomes of critically ill cancer patients with *Acinetobacter baumannii* (AB) infection.

METHODS: This was an observational study that included 23 consecutive cancer patients who acquired AB infections during their stay at ICU of the National Cancer Institute of Mexico (INCAN), located in Mexico City. Data collection took place between January 2011, and December 2012. Patients who had AB infections before ICU admission, and infections that occurred during the first 2 d of ICU stay were excluded. Data were obtained by reviewing the electronic health record of each patient. This investigation was approved by the Scientific and Ethics Committees at INCAN. Because of its observational nature, informed consent of the patients was not required.

RESULTS: Throughout the study period, a total of 494 critically ill patients with cancer were admitted to the ICU of the INCan, 23 (4.6%) of whom developed AB infections. Sixteen (60.9%) of these patients had hematologic malignancies. Most frequent reasons for ICU admission were severe sepsis or septic shock (56.2%) and postoperative care (21.7%). The respiratory tract was the most frequent site of AB infection (91.3%). The most common organ dysfunction observed in our group of patients were the respiratory (100%), cardiovascular (100%), hepatic (73.9%) and renal dysfunction (65.2%). The ICU mortality of patients with 3 or less organ system dysfunctions was 11.7% (2/17) compared with 66.6% (4/6) for the group of patients with 4 or more organ system dysfunctions ($P = 0.021$). Multivariate analysis identified blood lactate levels (BLL) as the only variable independently associated with in-ICU death (OR = 2.59, 95%CI: 1.04-6.43, $P = 0.040$). ICU and hospital mortality rates were 26.1% and 43.5%, respectively.

CONCLUSION: The mortality rate in critically ill patients with both HM, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a BLL ≥ 2.6 mmol/L in the first day of stay in the ICU.

Key words: Outcomes; Cancer patients; *Acinetobacter baumannii*; Intensive care; Critical care

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Several factors have been associated with poor prognosis among critically ill patients with infections caused by *Acinetobacter baumannii* (AB) in the intensive care unit (ICU) including renal failure, thrombocytopenia, neutropenia, history of prior immunosuppressive therapy use, the need for invasive mechanical ventilation, and development of severe sepsis. In this study the mortality rate in patients with both hematological malignancies, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a blood lactate levels ≥ 2.6 mmol/L in the first day of stay in the ICU.

Ñamendys-Silva SA, Correa-García P, García-Guillén FJ, González-Herrera MO, Pérez-Alonso A, Texcocano-Becerra J, Herrera-Gómez A, Cornejo-Juárez P, Meneses-García A. Outcomes of critically ill cancer patients with *Acinetobacter baumannii* infection. *World J Crit Care Med* 2015; 4(3): 258-264 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i3/258.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i3.258>

INTRODUCTION

Acinetobacter baumannii (AB) is an aerobic, gram-negative coccobacillary rod that grows at 20 °C-30 °C on standard laboratory media^[1]. AB infections may be

fatal in patients with suboptimal immune defenses^[2]. The mortality attributable to infections caused by AB in critically ill patients ranges from 40.7% to 73%^[3-5]. The intensive care unit (ICU) and hospital mortality rate of patients with both hematologic malignancies and AB infection is 83%^[6]; however, patients with solid tumors and bacteremia caused by AB have a relatively good prognosis with a mortality rate of 14.5%^[7].

Risk factors associated with AB colonization or infection include prolonged hospitalization, admission to the ICU, recent surgical procedures, exposure to antibiotics, use of central venous catheter, hospitalization and nursing home residence before hospital admission^[8]. Several factors have been associated with poor prognosis among critically ill patients with infections caused by AB in the ICU, including renal failure, thrombocytopenia^[9], low Glasgow coma scale, neutropenia, history of prior immunosuppressive therapy use, the need for mechanical ventilatory support, and development of severe sepsis^[6].

In Latin America *Acinetobacter* spp has been reported as one of the most commonly isolated species (9.6%) from patients with suspected hospital-acquired pneumonia^[10]. In Mexico, information on the prevalence and incidence of AB infections is limited^[11,12]. The aim of the present study was to describe the ICU outcomes of critically ill cancer patients with AB infection.

MATERIALS AND METHODS

This was an observational study that included 23 consecutive cancer patients who acquired AB infections during their stay at ICU of the National Cancer Institute of Mexico (INCan), located in Mexico City. Data collection took place between January 2011, and December 2012. Data on the characteristics, organization, and recommendations for admission to our ICU have been previously reported^[13,14]. Patients who had AB infections before ICU admission, and infections that occurred during the first 2 d of ICU stay were excluded. This investigation was approved by the Scientific and Ethics Committees at INCan (Rev/02/13). Because of its observational nature, informed consent of the patients was not required.

Data were obtained by reviewing the electronic health record of each patient. Data obtained included: the Eastern Cooperative Oncology Group scale for performance status^[15] prior to hospitalization, malignancy types, reasons for ICU admission, the need for invasive mechanical ventilation (IMV), the need for vasopressor therapy, durations of vasopressors, length of IMV, the length of stay (LOS) in the hospital before ICU admission, the LOS in hospital wards before ICU, use of antibiotics 30 d before ICU admission, infection sites, and the ICU and hospital mortality rate. The LOS in the ICU was measured by the number of hours or days spent there by the patient. The LOS in the hospital before ICU admission was quantified as the number of days from date of hospital admission until

ICU admission. The AB was categorized as follows: multidrug-resistant (MDR), pandrug-resistant (PDR), and pansensitive (PDS). AB MDR was defined as non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories. AB PDR was defined as non-susceptible to ≥ 1 agent in all but ≤ 2 categories. AB PDS was defined as susceptible to all antimicrobial agents^[16]. The Acute Physiology and Chronic Health Evaluation II score^[17], and the Sequential Organ Failure Assessment (SOFA) score^[18] were calculated within the first day ICU stay. In this study we have defined organ dysfunction as a SOFA score ≥ 1 point^[14]. Malignancies were grouped into either hematological malignancies (HM) or solid tumors. Patients were divided into two groups based on their blood lactate levels (BLL): BLL ≥ 2.6 mmol/L or BLL < 2.6 mmol/L.

Data presentation

The Kolmogorov-Smirnov test was performed to verify the normality of the distributions of the data; all of continuous variables were normally distributed. Data are presented as the mean \pm SD. The continuous variables were compared using student's *t* test and the chi-square or the Fisher exact test was used to compare categorical data.

Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve to evaluate the potential for using the lactate levels to discriminate between patients who die from those who survive. The sensitivity and specificity of the BLL cuoffs for predicting ICU mortality were examined. We constructed a multivariable model to identify factors associated with ICU mortality. We entered parameters into the model that were statistically significant on univariate analysis at a level of $P < 0.20$. Results were summarized as odds ratios (OR) with 95%CI. We assessed model discrimination using the area under the ROC curve^[19]. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and an adequate fit was assumed if $P > 0.05$ ^[20]. Survival curves were estimated by the Kaplan-Meier method and differences between survival curves were checked with the log-rank test. Statistical analysis was done using the Statistical Package for the Social Sciences version 20.0. All tests were two-tailed, and a $P < 0.05$ was predetermined for statistical significance. All reported *P* values are 2 sided.

Statistical analysis

The statistical methods of this study were reviewed by Silvio A Namendys-Silva, Department of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico City 14080, Mexico. Telephone: +52-55-47471020-13015, 13016.

RESULTS

Throughout the study period, a total of 494 patients with cancer were admitted to the ICU of the INCAN, 23 (4.6%) of whom developed AB infections. Sixteen

Table 1 Demographic and clinical characteristics of the study population

Characteristics	Values
No. of patients	23
Age (years), mean \pm SD	44.09 \pm 17.10
Gender (women), <i>n</i> (%)	11 (47.8)
Length of ICU stay (d), mean \pm SD	21.9 \pm 28.9
Length of hospital stay (d), mean \pm SD	23.9 \pm 12.3
Need for vasopressors, <i>n</i> (%)	23 (100)
Need for invasive mechanical ventilation, <i>n</i> (%)	23 (100)
Length of mechanical ventilation (d), mean \pm SD	21.4 \pm 11.8
In hospital ward time before ICU admission, <i>n</i> (%)	20 (86.9)
Length of stay in hospital wards before ICU admission (d), mean \pm SD	8.8 \pm 10.6
Use of antibiotics 30 days before ICU admission, <i>n</i> (%)	17 (73.9)
Infection site, <i>n</i> (%)	
Respiratory	21 (91.3)
Blood culture	3 (13)
Surgical site	1 (4.3)
Pansensitive, <i>n</i> (%)	2 (8.7)
Pandrug-resistant, <i>n</i> (%)	5 (21.7)
Multidrug-resistant, <i>n</i> (%)	16 (69.6)
APACHE II score, mean \pm SD	13.3 \pm 5.8
SOFA score, mean \pm SD	8.7 \pm 2.4
Performance status 0-2, <i>n</i> (%)	22 (95.7)
ICU mortality, <i>n</i> (%)	6 (26.1)
Hospital mortality, <i>n</i> (%)	10 (43.5)

ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IQR: Interquartile range; PEEP: Positive end expiratory pressure.

(60.9%) of these patients had HM. Most frequent reasons for ICU admission were severe sepsis or septic shock (56.2%) and postoperative care (21.7%). In Table 1 are presented demographic and clinical data of patients. The mean time between the admission to the ICU and the development of AB infection was 13 \pm 9.9 d. The respiratory tract was the most frequent site of AB infection (91.3%). The most frequent co-morbidity associated with AB infection was diabetes mellitus 3/23(13%), followed by cardiovascular disease (8.7%).

The most common organ dysfunction observed in our group of patients were the respiratory (100%), cardiovascular (100%), hepatic (73.9%) and renal dysfunction (65.2%). The ICU mortality of patients with 3 or less organ system dysfunctions was 11.7% (2/17) compared with 66.6% (4/6) for the group of patients with 4 or more organ system dysfunctions ($P = 0.021$) (Table 2).

The primary outcome variable of interest was ICU mortality. Univariate analysis indicated that the following three factors were associated with ICU death: BLL, four or more organ dysfunctions, and creatinine level (Table 3). Multivariate analysis identified BLL as the only variable independently associated with in-ICU death. The area under the ROC curve was 0.88 (95%CI: 0.74-0.99), $P = 0.006$, demonstrating a good discriminatory power to predict ICU mortality. The cut-off point was a BLL ≥ 2.6 mmol/L, with 100% sensitivity and 77% specificity (Figure 1). ICU and hospital mortality rates were 26.1% and 43.5%,

Table 2 Demographic and clinical characteristics of the critically ill cancer patients with *Acinetobacter baumannii* infection on the day of admission to the intensive care unit (initial) according to outcome

Characteristics	Survivors	Nonsurvivors	P
Age, years, mean \pm SD	42.6 \pm 16.6	48.1 \pm 19.3	0.510
Women, n (%)	8 (47)	3 (50)	0.901
APACHE II score, mean \pm SD	12.7 \pm 5.0	15.3 \pm 7.9	0.357
SOFA score, mean \pm SD	8.4 \pm 2.4	9.6 \pm 2.6	0.318
PEEP, cmH ₂ O	8.4 \pm 2.8	7.3 \pm 2.3	0.422
Durations of vasopressors	7.59 \pm 4.2	11 \pm 4.9	0.122
Leukocytes, $\times 10^9$ /L	8.6 \pm 6.9	11.6 \pm 13.1	0.487
Absolute neutrophil count, cells/mm ³	7.5 \pm 6.2	10.2 \pm 11.2	0.472
Lymphocytes, cells/mm ³	682 \pm 542	666 \pm 871	0.959
Platelets, $\times 10^9$ /L	184.4 \pm 149.2	112.8 \pm 105.0	0.291
Sodium, mmol/L	138 \pm 5.85	135.3 \pm 6.4	0.330
Potassium, mmol/L	3.9 \pm 0.51	4.0 \pm 0.71	0.800
Chloride, mmol/L	109.1 \pm 8.74	109.3 \pm 4.2	0.967
Lactate, mmol/L	2.01 \pm 1.29	5.2 \pm 3.2	0.002
Magnesium, mmol/L	0.93 \pm 0.24	0.97 \pm 0.13	0.722
Phosphorus, mmol/L	1.33 \pm 0.46	1.28 \pm 0.66	0.816
Hemoglobin, g/L	91.3 \pm 19.2	94.5 \pm 18.8	0.739
Creatinine, μ mol/L	75.8 \pm 39.01	133.2 \pm 34.4	0.004
Glucose, mmol/L	8.34 \pm 3.5	8.09 \pm 2.2	0.877
Bilirubin, total, μ mol/L	17.8 \pm 12.5	22.5 \pm 15.5	0.465
Uric acid, μ mol/L	219.0 \pm 94.0	189.3 \pm 149.0	0.576
ARDS, n (%)	13 (76.4)	4 (66.6)	0.632
Number of organ dysfunction (≥ 4)	2 (11.7)	4 (66.6)	0.021
Malignancies			
Hematological malignancy, n (%)	8 (47)	6 (100)	0.030
Solid tumor, n (%)	9 (52.9)	0 (0)	

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IQR: Interquartile range; PEEP: Positive end expiratory pressure; ARDS: Acute respiratory syndrome distress.

respectively. ICU survival by BLL is presented in Figure 2, indicating that the patients who had a BLL ≥ 2.6 mmol/L in the first day ICU stay were less likely to survive.

DISCUSSION

In this study, the incidence of AB infection in cancer patients who were admitted to the ICU was 4.6%, and ICU and hospital mortality rates were 26.1% and 43.5%, respectively, which is lower than the mortality rates reported by other authors^[4,6]. All of the patients who died had HM. Patients who had four or more organ system failures at the time of admission to the ICU had a high mortality rate. In the multivariate analysis, the only variable independently associated ICU mortality was a BLL ≥ 2.6 mmol/L. Patients with a BLL ≥ 2.6 mmol/L in the first day ICU stay were less likely to survive.

The overall ICU mortality rate found in our study could be related to the implementation of medical management protocols. Patients with severe sepsis and septic shock had received standard guidelines-based treatment^[21]. Patient care rounds were performed daily

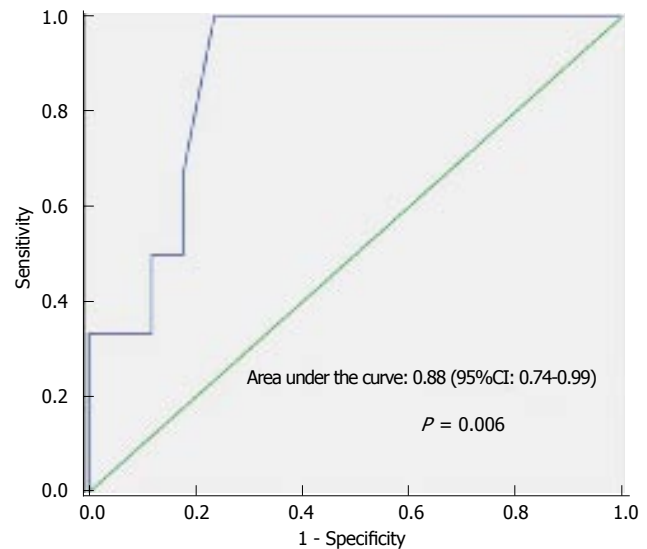


Figure 1 Receiver operator characteristic curve for lactate. The area under the Receiver operator characteristic curve is 0.88 (95%CI: 0.74-0.99), demonstrating a good discriminatory power for intensive care unit mortality.

with an infectious diseases attending physician^[22]. Levy and collaborators^[23] reported that the implementation of guidelines for management of severe sepsis and septic shock is associated with sustained, continuous quality improvement in sepsis care, and with a significant reduction in hospital mortality among patients with severe sepsis and septic shock.

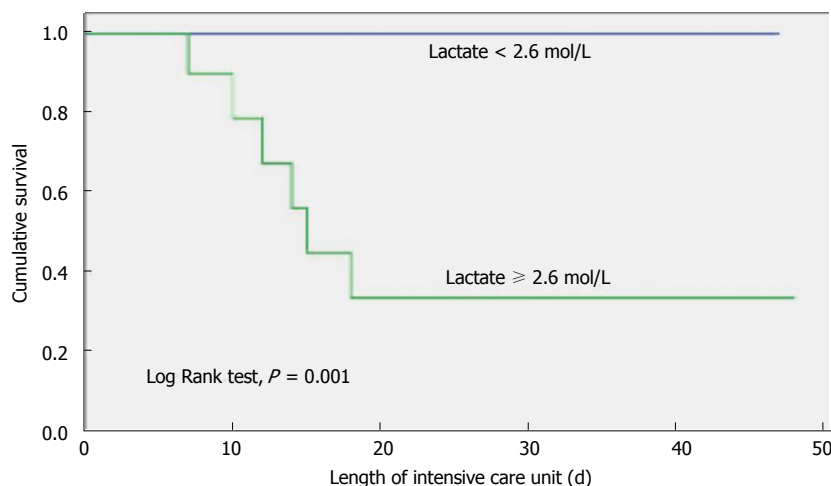
The patients with HM admitted to our ICU had higher ICU mortality rates than those with solid tumors (21.4% vs 46.1%)^[13,14]. Sepsis remains a frequent complication in patients with cancer, and is associated with high mortality^[24]. Immune dysfunction has been documented in patients with cancer. Predisposing factors for infection include the tumor site, intravenous devices, neutropenia because of an underlying disease, corticosteroids, monoclonal antibodies, and treatment with chemotherapy or radiation therapy^[25].

Risk factors for developing AB infections in patients with HM include advancing age, prior exposure to aminoglycosides, central venous catheterization, and the presence of nasogastric tube^[6]. Turkoglu *et al*^[6] reported that a low Glasgow coma scale, neutropenia, history of prior immunosuppressive therapy use, the need for IMV, and development of severe sepsis were associated with mortality in patients with HM. Infection with AB an APACHE II score ≥ 21 points are variables associated with a poor clinical outcomes for patients with solid tumors and AB complex bacteremia^[7]. In our study all of the patients who died in the ICU had HM, and required vasopressors. Univariate analysis primarily identified three factors that were related with ICU mortality; BLL, four or more organ dysfunctions, and creatinine levels. Multivariate analysis identified BLL as an independent prognostic factor for in-ICU death. The patients with BLL ≥ 2.6 mmol/L in the first day of stay in the ICU were less likely to survive. Increased BLL

Table 3 Univariate and multivariate logistic regression analysis for identifying independent risk factors for mortality in the intensive care unit

Variables	Univariate		P	Multivariate		P
	OR	95%CI		OR	95%CI	
Age (yr)	1.02	0.96-1.08	0.491			
Gender (male)	1.12	0.17-7.24	0.901			
APACHE II score	1.07	0.92-1.25	0.345			
SOFA score	1.23	0.82-1.84	0.308			
Length of stay in hospital wards before ICU admission (d)	0.76	0.51-1.12	0.171			
Duration of vasopressors (d)	1.18	0.95-1.48	0.129			
Blood lactate level (mmol/L)	2.59	1.04-6.43	0.04	2.59	1.04-6.43	0.04
Number of organ dysfunction (≥ 4)	15.00	1.58-142.1	0.018			
Creatinine ($\mu\text{mol/L}$)	1.03	1.004-1.064	0.024			
Total bilirubin ($\mu\text{mol/L}$)	1.02	0.95-1.10	0.449			
Albumin g/L	1.06	0.89-1.27	0.494			
Platelets ($\times 10^9/\text{L}$)	0.99	0.98-1.00	0.295			
Absolute neutrophil count/ μL	1.04	0.92-1.17	0.459			
Absolute lymphocytes count/ μL	1.03	0.93-1.15	0.479			

Goodness-of-fit (Hosmer-Lemeshow) $\chi^2 = 4.42$, $P = 0.817$, AUC = 0.88 (0.74-0.99), $P = 0.006$. APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval; AUC: Area under receiver operator characteristic curve.


Figure 2 Overall survival with respect to blood lactate level in the first 24 h of intensive care unit stay.

have been related to morbidity and mortality^[26]. BLL are frequently elevated in critically ill patients and correlate well with disease severity. Hyperlactatemia (> 2 mmol/L) is observed in shock states when oxygen consumption becomes critically dependent on oxygen delivery^[27]. The results of the current study suggest that in critically ill patients with cancer, and sepsis caused by AB, BLL may be used to identify patients at an increased risk of an adverse outcome. This may help to identify patients who may benefit from early admission to ICU. This report confirms that BLL is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection. There have been no new cases reported since July 2014 in our ICU.

This study has the following limitations: (1) The clinical data were obtained from a single institution; and (2) A small number of patients was included.

The mortality rate in critically ill patients with both HM, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a BLL ≥ 2.6 mmol/L in the first day of

stay in the ICU.

ACKNOWLEDGMENTS

We thank the nurses and medical staff of the intensive care unit at INCAN, Mexico City who were involved in the care of these patients for their assistance.

COMMENTS

Background

The mortality attributable to infections caused by *Acinetobacter baumannii* (AB) in critically ill patients ranges from 40.7% to 73%. The intensive care unit (ICU) and hospital mortality rate of patients with both hematologic malignancies and AB infection is high. Risk factors associated with AB colonization or infection include prolonged hospitalization, ICU admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization and nursing home residence. Several factors have been associated with poor prognosis among critically ill patients with infections caused by AB in the ICU, including renal failure, thrombocytopenia, the presence of neutropenia, prior immunosuppressive therapy, the need for invasive mechanical ventilation, and development of severe sepsis.

Research frontiers

In Latin America *Acinetobacter* spp has been reported as one of the most frequent species isolated from patients hospitalized with suspected pneumonia. In Mexico, information on the prevalence and incidence of AB infections is limited.

Innovations and breakthroughs

Blood lactate level (BLL) is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection and thereby the importance of providing ICU treatment.

Applications

The results of our study suggest that in critically ill cancer patients with sepsis caused by AB, BLL may be used to identify patients at an increased risk of an adverse outcome. This may help to identify patients who may benefit from early admission to ICU.

Peer-review

The manuscript is well conceived and indicates that lactate is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection and thereby the importance of providing ICU treatment.

REFERENCES

- 1 Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. *Clin Infect Dis* 2006; **42**: 692-699 [PMID: 16447117]
- 2 Montefour K, Frieden J, Hurst S, Helmich C, Headley D, Martin M, Boyle DA. *Acinetobacter baumannii*: an emerging multidrug-resistant pathogen in critical care. *Crit Care Nurse* 2008; **28**: 15-25; quiz 26 [PMID: 18238934]
- 3 Lee NY, Lee JC, Li MC, Li CW, Ko WC. Empirical antimicrobial therapy for critically ill patients with *Acinetobacter baumannii* bacteremia: combination is better. *J Microbiol Immunol Infect* 2013; **46**: 397-398 [PMID: 23632604 DOI: 10.1016/j.jmii.2013.03.004]
- 4 Prates CG, Martins AF, Superti SV, Lopes FS, Ramos F, Cantarelli VV, Zavascki AP. Risk factors for 30-day mortality in patients with carbapenem-resistant *Acinetobacter baumannii* during an outbreak in an intensive care unit. *Epidemiol Infect* 2011; **139**: 411-418 [PMID: 20513254 DOI: 10.1017/S0950268810001238]
- 5 Fagon JY, Chastre J, Domart Y, Trouillet JL, Gibert C. Mortality due to ventilator-associated pneumonia or colonization with *Pseudomonas* or *Acinetobacter* species: assessment by quantitative culture of samples obtained by a protected specimen brush. *Clin Infect Dis* 1996; **23**: 538-542 [PMID: 8879777]
- 6 Turkoglu M, Mirza E, Tunçan OG, Erdem GU, Dizbay M, Yağcı M, Aygencel G, Türköz Sucak G. *Acinetobacter baumannii* infection in patients with hematologic malignancies in intensive care unit: risk factors and impact on mortality. *J Crit Care* 2011; **26**: 460-467 [PMID: 21715136 DOI: 10.1016/j.jcrc.2011.04.007]
- 7 Chiang MC, Kuo SC, Chen SJ, Yang SP, Lee YT, Chen TL, Fung CP. Clinical characteristics and outcomes of bacteremia due to different genomic species of *Acinetobacter baumannii* complex in patients with solid tumors. *Infection* 2012; **40**: 19-26 [PMID: 21887526 DOI: 10.1007/s15010-011-0187-4]
- 8 Fishbain J, Peleg AY. Treatment of *Acinetobacter* infections. *Clin Infect Dis* 2010; **51**: 79-84 [PMID: 20504234 DOI: 10.1086/653120]
- 9 Katsaragakis S, Markogiannakis H, Samara E, Pachylaki N, Theodoraki EM, Xanthaki A, Toutouza M, Toutouzas KG, Theodorou D. Predictors of mortality of *Acinetobacter baumannii* infections: A 2-year prospective study in a Greek surgical intensive care unit. *Am J Infect Control* 2010; **38**: 631-635 [PMID: 20471716 DOI: 10.1016/j.ajic.2010.01.009]
- 10 Gales AC, Sader H HS, Jones RN. Respiratory tract pathogens isolated from patients hospitalized with suspected pneumonia in Latin America: frequency of occurrence and antimicrobial susceptibility profile: results from the SENTRY Antimicrobial Surveillance Program (1997-2000). *Diagn Microbiol Infect Dis* 2002; **44**: 301-311 [PMID: 12493178]
- 11 Garza-González E, Llaca-Díaz JM, Bosques-Padilla FJ, González GM. Prevalence of multidrug-resistant bacteria at a tertiary-care teaching hospital in Mexico: special focus on *Acinetobacter baumannii*. *Chemotherapy* 2010; **56**: 275-279 [PMID: 20693798 DOI: 10.1159/000319903]
- 12 Llaca-Díaz JM, Mendoza-Olazarán S, Camacho-Ortiz A, Flores S, Garza-González E. One-year surveillance of ESKAPE pathogens in an intensive care unit of Monterrey, Mexico. *Chemotherapy* 2012; **58**: 475-481 [PMID: 23548324 DOI: 10.1159/000346352]
- 13 Namendys-Silva SA, Texcocano-Becerra J, Herrera-Gómez A. Prognostic factors in critically ill patients with solid tumours admitted to an oncological intensive care unit. *Anaesth Intensive Care* 2010; **38**: 317-324 [PMID: 20369766]
- 14 Namendys-Silva SA, González-Herrera MO, García-Guillén FJ, Texcocano-Becerra J, Herrera-Gómez A. Outcome of critically ill patients with hematological malignancies. *Ann Hematol* 2013; **92**: 699-705 [PMID: 23328791 DOI: 10.1007/s00277-013-1675-7]
- 15 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655 [PMID: 7165009]
- 16 Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268-281 [PMID: 21793988 DOI: 10.1111/j.1469-0691.2011.03570.x]
- 17 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249]
- 18 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239]
- 19 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29-36 [PMID: 7063747]
- 20 Hosmer DW, Taber S, Lemeshow S. The importance of assessing the fit of logistic regression models: a case study. *Am J Public Health* 1991; **81**: 1630-1635 [PMID: 1746660]
- 21 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580-637 [PMID: 23353941 DOI: 10.1097/CCM.0b013e31827e83af]
- 22 Namendys-Silva SA, González-Herrera MO, Texcocano-Becerra J, Herrera-Gómez A. Clinical characteristics and outcomes of critically ill cancer patients with septic shock. *QJM* 2011; **104**: 505-511 [PMID: 21258055 DOI: 10.1093/qjmed/hcq260]
- 23 Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; **38**: 367-374 [PMID: 20035219 DOI: 10.1097/CCM.0b013e3181cb0cdc]
- 24 Rosolem MM, Rabello LS, Lisboa T, Caruso P, Costa RT, Leal JV, Salluh JI, Soares M. Critically ill patients with cancer and sepsis: clinical course and prognostic factors. *J Crit Care* 2012; **27**: 301-307 [PMID: 21855281 DOI: 10.1016/j.jcrc.2011.06.014]
- 25 Rapoport BL. Management of the cancer patient with infection and neutropenia. *Semin Oncol* 2011; **38**: 424-430 [PMID: 21600373 DOI: 10.1053/j.seminoncol.2011.03.013]

- 26 **Bakker J**, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care* 2013; **3**: 12 [PMID: 23663301 DOI: 10.1186/2110-5820-3-12]
- 27 **Okorie ON**, Dellinger P. Lactate: biomarker and potential therapeutic target. *Crit Care Clin* 2011; **27**: 299-326 [PMID: 21440203 DOI: 10.1016/j.ccc.2010.12.013]

P- Reviewer: Boucek C, Krishnan T, Nagata T **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



World Journal of *Critical Care Medicine*

World J Crit Care Med 2015 November 4; 4(4): 265-301



Editorial Board

2011-2015

The *World Journal of Critical Care Medicine* Editorial Board consists of 246 members, representing a team of worldwide experts in critical care medicine. They are from 45 countries, including Argentina (2), Australia (8), Austria (2), Bangladesh (1), Belgium (3), Brazil (4), Canada (7), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (8), Germany (11), Greece (9), Hungary (1), India (10), Iran (2), Ireland (1), Israel (6), Italy (14), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (3), Singapore (1), Slovenia (1), South Africa (1), Spain (7), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (8), United States (72), and Uruguay (1).

EDITOR-IN-CHIEF

Yaseen Mohamed Arabi, *Riyadh*

GUEST EDITORIAL BOARD MEMBERS

Hsing I Chen, *Hualien*
Sheng-Hsien Chen, *Tainan*
Yih-Sharnng Chen, *Taipei*
Yung-Chang Chen, *Taipei*
Der-Yang Cho, *Taichung*
Cheng-Keng Chuang, *Taoyuan*
How-Ran Guo, *Tainan*
Bang-Gee Hsu, *Hualien*
Chien-Wei Hsu, *Kaohsiung*
Wen-Jinn Liaw, *Taipei*
Yan-Ren Lin, *Changhua*
Jiunn-Jye Sheu, *Kaohsiung*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Eduardo Chuluyan, *Buenos Aires*
Adrian Angel Inchauspe, *Berazategui*



Australia

Zsolt J Balogh, *Newcastle*
Zoltan Huba Endre, *Sydney*
Nam Q Nguyen, *Adelaide*
Alistair D Nichol, *Melbourne*
Srinivas Rajagopala, *Adelaide*
Georg Marcus Schmolzer, *Melbourne*
Andrew Trevitt Slack, *Southport*
Ravindranath Tiruvoipati, *Frankston*



Austria

Lars-Peter Kamolz, *Vienna*
Sylvia Knapp, *Vienna*



Bangladesh

Saidur Rahman Mashreky, *Dhaka*



Belgium

Teresinha Leal, *Brussels*
Manu Malbrain, *Antwerp*
Jean-Louis Vincent, *Brussels*



Brazil

Luciano CP Azevedo, *São Paulo*
Patricia Rieken Macedo Rocco, *Rio de Janeiro*
Marcos Antonio Rossi, *São Paulo*
Renato Seligman, *Porto Alegre*



Canada

Douglas D Fraser, *London*
Pierre A Guertin, *Quebec*
Marc Jeschke, *Toronto*
Constantine J Karvellas, *Edmonton*
Wolfgang Michael Kuebler, *Toronto*
Mingyao Liu, *Toronto*
Xi Yang, *Manitoba*



China

Xiang-Dong Chen, *Chengdu*

Xu-Lin Chen, *Hefei*
Wong Tak Chuen, *Hong Kong*
Ming-Xu Da, *Gansu*
Huang-Xian Ju, *Nanjing*
Ting-Bo Liang, *Hangzhou*
Peng-Lin Ma, *Beijing*
Chung-Wah David Siu, *Hong Kong*
Yong-Ming Yao, *Beijing*
Jia-Ping Zhang, *Chongqing*
Wei-Dong Zhou, *Beijing*



Croatia

Alan Sustic, *Rijeka*



Cuba

Jesús Pérez-Nellar, *La Habana*



Denmark

Dan Stieper Karbing, *Aalborg*



Egypt

Ibrahim Abouomira, *Cairo*
Hanan Ibrahim, *Cairo*
Amr M Moghazy, *Alexandria*
Ayman A Yousef, *Tanta*



Finland

Asko Armas Riutta, *Tampere*

**France**

Jean-Marc Cavaillon, *Paris*
 Jean-Michel Constantin, *Clermont-Ferrand*
 Marc Leone, *Marseille*
 Bruno Mégarbane, *Paris*
 Saad Nseir, *Lille*
 Nicolas Terzi, *Caen*
 Jean-François Timsit, *La Tronche Cedex*
 Benoit Vallet, *Lille*

**Germany**

Hendrik Bracht, *Ulm*
 Michael Czaplik, *Aachen*
 Gerrit Grieb, *Aachen*
 Tobias Keck, *Freiburg*
 Philipp Kobbe, *Aachen*
 Alexander Koch, *Aachen*
 Marc Maegele, *Cologne*
 Norbert Pallua, *Aachen*
 Andrzej Antoni Piatkowski, *Aachen*
 Armin Rudolf Sablotzki, *Leipzig*
 Kai D Zacharowski, *Frankfurt am Main*

**Greece**

Ioanna Dimopoulou, *Athens*
 Dimitrios Karakitsos, *Athens*
 Petros Kopterides, *Athens*
 Gregory Kouraklis, *Athens*
 Athanasios D Marinis, *Athens*
 George Nakos, *Ioannina*
 Papaioannou E Vasilios, *Alexandroupolis*
 Theodoros Xanthos, *Athens*
 Spyros G Zakyntinos, *Athens*

**Hungary**

Zoltan Rakonczay, *Szeged*

**India**

Rachna Agarwal, *Delhi*
 Ritesh Agarwal, *Chandigarh*
 Mohammad Farooq Butt, *Srinagar*
 Mohan Gurjar, *Lucknow*
 Deven Juneja, *New Delhi*
 Farhad N Kapadia, *Mumbai*
 Vikram Kate, *Pondicherry*
 Pramod Kumar, *Manipal*
 Ritesh G Menezes, *Mangalore*
 Medha Mohta, *Delhi*

**Iran**

Hemmat Maghsoudi, *Tabriz*
 Homayoun Sadeghi-Bazargani, *Tabriz*

**Ireland**

Sanjay H Chotirmall, *Dublin*

**Israel**

Alexander Becker, *Kefar Tavor*
 Yoram Kluger, *Haifa*
 Yona Kosashvili, *Zerrifin*
 Kobi Peleg, *Tel Aviv*
 Ilan Sela, *Rehovot*
 Pierre Singer, *Tel Aviv*

**Italy**

Giacomo Bellani, *Monza*
 Giovanni Camussi, *Torino*
 Anselmo Caricato, *Rome*
 Piero Ceriana, *Pavia*
 Antonio Chiaretti, *Rome*
 Davide Chiumello, *Milano*
 Alfredo Conti, *Messina*
 Paolo Cotogni, *Torino*
 Daniele M De Luca, *Rome*
 Vincenzo De Santis, *Rome*
 Luca La Colla, *Parma*
 Giovanni Landoni, *Milano*
 Raffaele Scala, *Lucca*
 Giovanni Vento, *Rome*

**Japan**

Keishiro Aoyagi, *Kurume*
 Satoshi Hagiwara, *Yufu*
 Yuichi Hattori, *Toyama*
 Hideo Inaba, *Kanazawa*
 Eisuke Kagawa, *Hiroshima*
 Chieko Mitaka, *Tokyo*

**Jordan**

Feras Ibrahim Hawari, *Amman*

**Mexico**

Silvio A Ñamendys-Silva, *Mexico City*

**Morocco**

Redouane Abouqal, *Rabat*

**Netherlands**

WA Buurman, *Maastricht*
 Martin CJ Kneyber, *Groningen*
 Patrick Schober, *Amsterdam*
 Arie Barend Van Vugt, *Enschede*

**New Zealand**

Sultan Zayed Al-Shaqsi, *Dunedin*
 Arman Adam Kahokehr, *Whangarei*
 John William Pickering, *Christchurch*

**Norway**

Ulf R Dahle, *Oslo*

**Poland**

Maciej Owecki, *Poznań*

**Portugal**

Ernestina Rodrigues Gomes, *Porto*
 Cristina Granja, *Porto*
 José António Lopes, *Lisbon*
 Pedro M Póvoa, *Lisbon*

**Russia**

Konstantin A Popugaev, *Moscow*

**Saudi Arabia**

Imran Khalid, *Jeddah*
 Mohamed Taifour Suliman, *Tabuk*

**Singapore**

Devanand Anantham, *Singapore*

**Slovenia**

Štefek Grmec, *Maribor*

**South Africa**

DL Clarke, *Pietermaritzburg*

**Spain**

Juan Carlos Montejo González, *Madrid*
 David Jimenez, *Madrid*
 Juan Antonio Llompарт-Pou, *Palma*
 Antonio Torres Mart, *Barcelona*
 Enrique Ariel Piacentini, *Barcelona*
 Alonso Mateos Rodriguez, *Madrid*
 R Rodríguez-Roisin, *Barcelona*

**Sweden**

Mihai Oltean, *Gothenburg*

**Switzerland**

Dieter Cadosch, *Zurich*
 Mihael Potocki, *Basel*
 John Friedrich Stover, *Zurich*



Thailand

Viroj Wiwanitkit, *Bangkok*



Tunisia

Mabrouk Bahloul, *Sfax*



Turkey

Yusuf Kenan Coban, *Malatya*
Bensu Karahalil, *Ankara*
Ali Nayci, *Mersin*



United Kingdom

Sammy Al-Benna, *Nottingham*
Giles N Cattermole, *London*
Frantisek Duska, *Nottingham*
James Nicholas Fullerton, *London*
Christina Jones, *Prescot*
Sameer Khan, *Middlesbrough*
George Ntoumenopoulos, *London*
Cecilia O'Kane, *Belfast*



United States

Edward Abraham, *Winston-Salem*
Bernard R Bendok, *Chicago*
Michael Blaivas, *Atlanta*

Charles D Boucek, *Pittsburgh*
Marcia Leigh Brackbill, *Winchester*
Ronald A Bronicki, *Houston*
Robert C Cantu, *Concord*
Marylou Cardenas-Turanzas, *Houston*
Archana Chatterjee, *Omaha*
Paul A Checchia, *St. Louis*
Rubin Issam Cohen, *New Hyde Park*
Stephen Cohn, *San Antonio*
Donald Edward Craven, *Burlington*
Ruy J Cruz Jr, *Pittsburgh*
Francis C Dane, *Roanoke*
Marc de Moya, *Boston*
Steven M Donn, *Ann Arbor*
Christopher P Farrell, *Wynnewood*
Marco Fernández, *Nashville*
Kevin Foster, *Phoenix*
Barry D Fuchs, *Philadelphia*
Richard P Gonzalez, *Mobile*
Kenneth W Gow, *Seattle*
Alan H Hall, *Laramie*
Jijo John, *Oklahoma City*
Lewis J Kaplan, *New Haven*
Jason N Katz, *Chapel Hill*
Salah Georges Keyrouz, *Little Rock*
Deborah A Kuhls, *Las Vegas*
Gregory Luke Larkin, *New Haven*
Christos Lazaridis, *Charleston*
James Anthony Lin, *Los Angeles*
Yahia M Lodi, *Syracuse*
Roger M Loria, *Richmond*
Aigang Lu, *Cincinnati*
Rudolf Lucas, *Augusta*
O John Ma, *Portland*
Robert T Mallet, *Fort Worth*
William T McGee, *Springfield*
Mark G McKenney, *Miami*

Michael Moussouttas, *Philadelphia*
Oliver Hans-Josef Muensterer, *Birmingham*
Rahul Nanchal, *Milwaukee*
Michael Steven Niederman, *Mineola*
Gary Frank Nieman, *Syracuse*
James Martin O'Brien, *Columbus*
Martin Oudega, *Pittsburgh*
Catherine Mobley Preissig, *Duluth*
Virginia Prendergast, *Phoenix*
Ramesh Raghupathi, *Philadelphia*
Miren Ava Schinco, *Jacksonville*
Carl Ivan Schulman, *Miami*
L Keith Scott, *Shreveport*
Kevin Navin Sheth, *Baltimore*
Jenni Short, *Salina*
Ronald Fong Sing, *Charlotte*
Philip Charles Spinella, *St. Louis*
Robert M Starke, *Charlottesville*
Stanislaw Peter A Stawicki, *Columbus*
David Christopher Stockwell, *Washington*
Stanislav Svetlov, *Gainesville*
Maged A Tanios, *Long Beach*
Neal James Thomas, *Hershey*
Nancy Moon Tofil, *Birmingham*
Balagangadhar R Totapally, *Miami*
Steven Nicholas Vaslef, *Durham*
Joseph Clark Watson, *Falls Church*
John Stephen Wilgis, *Orlando*
David Conrad Willms, *San Diego*
Haodong Xu, *Rochester*
Xiao-Ming Xu, *Indianapolis*
Midori Anne Yenari, *San Francisco*



Uruguay

William Manzanares, *Montevideo*



Contents

Quarterly Volume 4 Number 4 November 4, 2015

EDITORIAL

- 265 Deep sternal wound infection after cardiac surgery: Evidences and controversies
Cotogni P, Barbero C, Rinaldi M
- 274 Why there is a need to discuss pulmonary hypertension other than pulmonary arterial hypertension?
Papathanasiou A, Nakos G

MINIREVIEWS

- 278 Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way
Santos RS, Silva PL, Pelosi P, Rocco PRM

ORIGINAL ARTICLE

Basic Study

- 287 *In vivo* analysis of intestinal permeability following hemorrhagic shock
Alsaigh T, Chang M, Richter M, Mazor R, Kistler EB

Retrospective Study

- 296 Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury
O'Phelan KH, Merenda A, Denny KG, Zaila KE, Gonzalez C

Contents

World Journal of Critical Care Medicine
Volume 4 Number 4 November 4, 2015

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Adrian Angel Inchauspe, MD, Surgery Professor, Acupuncture Professor, Calle 14 N*4079, Berazategui, Provincia de Buenos Aires CP 1884, Argentina

AIM AND SCOPE

World Journal of Critical Care Medicine (World J Crit Care Med, WJCCM), online ISSN 2220-3141, DOI: 10.5492 is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, and application of bronchofiberscopy in critically ill patients.

We encourage authors to submit their manuscripts to *WJCCM*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Critical Care Medicine is now indexed in PubMed Central, PubMed, Digital Object Identifier.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Su-Qing Liu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Yaseen Mohamed Arabi, MD, FCCP, FCCM, Associate Professor, Chairman, Intensive Care Department, King Saud Bin Abdulaziz University, Medical Director, Respiratory Services, King Abdulaziz Medical City, National Guard Hospital, Riyadh, PO Box 22490, Riyadh 11426, Saudi Arabia

Derek S Wheeler, MD, FAAP, FCCP, FCCM, Associate Professor, Associate Patient Safety Officer, Medical Director, Pediatric Intensive Care Unit, Division of Critical Care Medicine, James M. Anderson Center for Health Systems Excellence, The Center for Simulation and Research, Co-Director, The Center

for Acute Care Nephrology, Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, United States

EDITORIAL OFFICE

Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.wjnet.com/esps/helpdesk.aspx>

<http://www.wjnet.com>

PUBLICATION DATE

November 4, 2015

COPYRIGHT

© 2015 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at http://www.wjnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION

<http://www.wjnet.com/esps/>

Deep sternal wound infection after cardiac surgery: Evidences and controversies

Paolo Cotogni, Cristina Barbero, Mauro Rinaldi

Paolo Cotogni, Anesthesiology and Intensive Care, Department of Medicine, S. Giovanni Battista Hospital, University of Turin, 10123 Turin, Italy

Cristina Barbero, Mauro Rinaldi, Department of Cardiovascular and Thoracic Surgery, S. Giovanni Battista Hospital, University of Turin, 10123 Turin, Italy

Author contributions: Cotogni P and Barbero C developed the research question and review design, drafted and finalized the manuscript; Rinaldi M revised it critically for important intellectual content; all authors approved the final version.

Conflict-of-interest statement: The authors have no conflict of interests.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Paolo Cotogni, MD, MSc, Anesthesiology and Intensive Care, Department of Medicine, S. Giovanni Battista Hospital, University of Turin, Via Giovanni Giolitti 9, 10123 Turin, Italy. paolo.cotogni@unito.it
Telephone: +39-11-5171634
Fax: +39-11-6334324

Received: May 30, 2015

Peer-review started: May 30, 2015

First decision: August 14, 2015

Revised: September 18, 2015

Accepted: October 12, 2015

Article in press: October 13, 2015

Published online: November 4, 2015

Abstract

Despite many advances in prevention and perioperative

care, deep sternal wound infection (DSWI) remains a pressing concern in cardiac surgery, with a still relevant incidence and with a considerable impact on in-hospital mortality and also on mid- and long-term survival. The permanent high impact of this complication is partially related to the increasing proportion of patients at high-risk for infection, as well as to the many patient and surgical risk factors involved in the pathogenesis of DSWI. The prophylactic antibiotic therapy is one of the most important tools in the prevention of DSWI. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial. The treatment of DSWI ranges from surgical revision with primary closure to surgical revision with open dressings or closed irrigation, from reconstruction with soft tissue flaps to negative pressure wound therapy (NPWT). However, to date, there have been no accepted recommendations regarding the best management of DSWI. Emerging evidence in the literature has validated the efficacy and safety of NPWT either as a single-line therapy, or as a "bridge" prior to final surgical closure. In conclusion, the careful control of patient and surgical risk factors - when possible, the proper antimicrobial prophylaxis, and the choice of validated techniques of treatment could contribute to keep DSWIs at a minimal rate.

Key words: Risk factors; Sternotomy; Wound healing; Wound infection; Postoperative care

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Intensivists and cardiothoracic surgeons are commonly worried about surgical site infections due to increasing length of stay, costs, and mortality. In particular, deep sternal wound infection (DSWI) is a worrying complication after cardiac surgery, with a still relevant incidence. Unfortunately, DSWI appearance is related to a wide number of both patient and surgical factors. This review may be useful for guiding

physicians to the knowledge of main risk factors and the choice of the appropriate management of DSWIs with the aim of reducing the rate of this potentially devastating complication in cardiac surgery patients.

Cotogni P, Barbero C, Rinaldi M. Deep sternal wound infection after cardiac surgery: Evidences and controversies. *World J Crit Care Med* 2015; 4(4): 265-273 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i4/265.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i4.265>

INTRODUCTION

Deep sternal wound infection (DSWI) is one of the most complex and potentially devastating complications following median sternotomy in cardiac surgery with a significant impact on both patient prognosis and hospital budgets^[1-5]. Despite many advances in prevention, it still remains significant and ranges between 0.5% and 6.8%^[6-10], with in-hospital mortality rates between 7% and 35%^[2,3,7,9,11-13]. Moreover, mid- and long-term survival is significantly reduced in patients that have experienced DSWI. By the end of the first year, Filsoufi *et al*^[6] found a 15% absolute survival difference between patients without DSWI and those who had developed this complication. In a 10-year follow-up study after coronary artery bypass grafting, the adjusted survival rate was 39% for patients who developed DSWI compared with 70% in patients who did not^[14]. Excess costs arise primarily owing to additional antibiotic treatments and surgical procedures, as well as increased hospital length of stay^[13,15].

The management of DSWI has progressed through long-lasting clinical experience. Commonly adopted strategies of treatment include surgical revision with primary closure, surgical revision with open dressings or closed irrigation, reconstruction with soft tissue flaps, and application of negative pressure wound therapy (NPWT)^[16-18]. However, at the moment, there has been no general consensus regarding the appropriate management of DSWI.

DEFINITION

According to Centers for Disease Control and Prevention (CDC) guidelines, the definition of a DSWI requires positive culture results of surgical sites or drainage from the mediastinal area or evidence of infection during surgical re-exploration or fever, sternal instability, and positive blood culture results^[19].

RISK FACTORS

Patient and surgical factors contribute to the risk of DSWI after cardiothoracic surgery. Patient factors include age^[20-22], female sex^[20,22,23], obesity^[2,4,20,21,24-28], diabetes

mellitus or hyperglycemia during the perioperative period^[2,20,21,24,26-29], smoking tobacco^[2,4,28-30], recent treatment with antibiotics^[31], *Staphylococcus aureus* nasal carriage^[32,33], skin infection anywhere on the body^[31], chronic obstructive pulmonary disease^[25,27], heart failure^[2,34], kidney dysfunction^[27,34], peripheral vascular disease^[2,26], and emergent or urgent surgery^[28,35].

The reason for the increased risk of DSWI in obese patients can be related to the poor perfusion of subcutaneous adipose layers with low levels of prophylactic antibiotics in this tissue. Gummert *et al*^[24] found a 1.5-times increased adjusted risk of DSWI after cardiac surgery in patients with body mass index > 30 kg/m². Filsoufi *et al*^[6] reported that obesity was associated with a more than 2-fold increased risk of DSWI.

Convincing evidence has emerged that the control of blood glucose levels during surgery and the immediate postoperative period with frequent monitoring and protocols for continuous intravenous administration of insulin can decrease DSWI rate^[36,37]. Researchers at the Mayo Clinic concluded that a 20 mg/dL (1.11 mmol/L) increase in the mean intraoperative blood glucose level correlated with an increase of more than 30% in adverse outcomes^[38]. A large prospective study of diabetic patients undergoing cardiac surgery demonstrated that hyperglycemia was an independent risk factor for death, length of hospital stay, and infection rates, and found that a continuous insulin infusion reduced these risks^[39].

Smoking tobacco can impair the tissue microcirculation and increase the risk of DSWI. Møller *et al*^[40] showed that preoperative cessation of smoking 6-8 wk prior to operation significantly reduced the infection rate in a prospective randomized trial in orthopedic prosthesis surgery. Actually, the CDC guidelines recommend smoking cessation at least 30 d prior to surgery^[19].

The patient's carriage of *Staphylococcus aureus* on skin and nares has been identified as an important risk factor for DSWI^[32,33]. The Society of Thoracic Surgeons practice guidelines upon antimicrobial prophylaxis recommend routine 5-d mupirocin 2% nasal administration for all patients undergoing cardiac surgery in the absence of a documented negative testing for staphylococcal colonization^[41]. However, concerns still remain about the extensive use of mupirocin because of lack of efficacy, risk of widespread high-level resistance, and costs^[42-44]. A systematic review of the literature and meta-analysis by Kallen *et al*^[45] demonstrated a 45% reduction in surgical site infections (SSIs) caused by *Staphylococcus aureus* with the use of preoperative mupirocin among cardiac surgery patients known to be colonized with *Staphylococcus aureus*. Of note, the only prospective, randomized, and double-blinded trial of mupirocin in cardiac surgery patients did not show benefit: No patients with poststernotomy mediastinitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) had identical isolates in preoperative and surgical-site cultures^[46].

Surgical risk factors include prolonged duration of aortic cross clamp, cardiopulmonary bypass perfusion or overall surgery^[22,26], use of internal mammary artery (IMA) grafts-especially bilaterally^[2,24,25,27,30], inadvertent paramedian sternotomy^[47], use of bone wax, extensive use of electrocauterization^[27], surgical procedures requiring prosthesis implant, use of intra-aortic balloon pump or ventricular assist device^[23,27], postoperative bleeding^[10], blood transfusions, re-exploration for bleeding^[6,23,24,48,49], re-operation, postoperative respiratory failure with prolonged mechanical ventilation^[2,6], and prolonged stay in intensive care unit (ICU)^[4,24,26].

Controversial opinions still remain on the IMA harvest technique. The skeletonization harvest technique is already known to severely reduce the incidence of DSWI - particularly in diabetic and obese patients - because of the better preservation of collateral sternal blood flow and internal thoracic veins^[50]. However, many cardiothoracic surgeons are reluctant to application this technique as it can easily lead to graft conduit damage^[51]. Evidences also suggest the need for dosing adjustment following IMA harvesting as this significantly diminishes antibiotic penetration into the presternal tissue^[52].

Level of concern has varied regarding to the risk of DSWI due to use of bone wax. Animal studies showed an increased risk of *Staphylococcus aureus* infections^[53]; however, a prospective, randomized trial of 400 patients found no detrimental effects^[54].

Finally, adherence to basic principles of care contributes to reduce the risk of DSWI. These mainly include reduced preoperative hospital stay, increased perioperative oxygenation, preoperative showering using antiseptic solution, hair removal over the operating site using scissors or a depilatory cream instead of shaving, and scrubbing of the operation site with a proper antiseptic solution and letting it dry^[6,19,31,55]. Chlorhexidine-, alcohol- or povidone-iodine-based solutions can be used; indeed, the CDC guidelines do not recommend one antiseptic solution over the others^[19].

PATHOGENS

Recent reports focused on a growing number of DSWIs caused by methicillin-resistant Gram-positive pathogens^[56]. *Staphylococcus epidermidis* is one of the most common agents in poststernotomy mediastinitis when foreign materials such as prosthetic heart valve are implanted; moreover, approximately 75% of the *Staphylococcus epidermidis* strains are methicillin-resistant^[57]. The other major pathogen in poststernotomy mediastinitis is *Staphylococcus aureus*. The latter microorganism has been increasingly associated with colonization of the patients' nares. National Nosocomial Infections Surveillance System reports that the rate of MRSA has risen from 30% in 1989 to 60% in 2005 in ICU patients with nosocomial infections and MRSA was the causative microorganism in a third of the patients with DSWI^[58].

ANTIMICROBIAL PROPHYLAXIS

The advantages of proper antimicrobial prophylaxis in patients undergoing cardiac surgery have been clearly demonstrated^[19,59,60]. However, the choice of antibiotic, the dose, the duration, the adequate levels in serum and tissue, and the timing of antimicrobial prophylaxis are still controversial^[11,41,61].

The Society of Thoracic Surgeons Practice Guidelines on antimicrobial prophylaxis in cardiac surgery recommended that a cephalosporin should be given within 60 min from the skin incision and be continued for 24-72 h^[41,61]. First generation (cefazolin), second generation (cefamandole and cefuroxime), and third generation (cefotaxime) cephalosporins have been shown to be effective in reducing SSIs in cardiac surgery; however, the superiority of one class over another has not been proven^[62-64].

The frequent identification of MRSA as the cause of DSWI has brought the attention on vancomycin as the prophylactic drug of choice^[10]. Engelman *et al.*^[41] stated that vancomycin is reserved mainly for patients with a history of type I allergic reaction to β -lactam agents or in the setting of the institutional presence of a "high incidence" of MRSA (class II B recommendation, level of evidence C). Vancomycin should be given with any of the following doses: 1000 mg, 1500 mg, or 15 mg/kg over 1 h, with completion within 1 h of the skin incision^[41]. The reason for the 1-h infusion is related to the risk of histamine-release phenomenon characterized by extensive erythematous rash that involves the upper chest and face ("red man syndrome") that can be triggered by a rapid infusion of vancomycin^[41,61]. Moreover, studies in the literature showed that the incidence of infection is decreased when the preoperative dose is administered within 1 h before surgical incision^[11,65]. Regarding the duration, postoperative prophylactic antibiotics are given for 48 h or less (class II A recommendation, level of evidence B)^[61].

A meta-analysis comparing cephalosporins with glycopeptides as antimicrobial prophylaxis regimens found a higher frequency of postoperative SSIs and a trend toward an increased risk of Gram-positive SSI in the glycopeptide group but a lower frequency of SSIs caused by resistant gram-positive pathogens^[66].

The relationship between timing of prophylactic antimicrobial administration and risk of infection is an additional field of debate. The 2011 American College of Cardiology/American Heart Association guidelines for cardiac surgery recommend that "Antibiotic prophylaxis should be initiated 30 to 60 min before surgery"^[9]. Key studies have demonstrated that antimicrobial prophylaxis administered too late or too early reduces the efficacy of the antimicrobial prophylaxis and increases the risk of infection^[10,11,65,67]; conversely, other reports do not clearly demonstrated the superiority of the 1-h window^[68-70].

Ideally, short courses of antimicrobial prophylaxis are preferred over longer courses to reduce costs, drug

toxicity, infection with *Clostridium difficile*, and the appearance of resistant pathogens^[11,19,61,65,71]. However, the use of cardiopulmonary bypass, the hypothermia, the length of operation, the high mortality and costs of DSWI suggest to prolonging the antimicrobial prophylaxis in cardiac surgery. A 2011 systematic review and meta-analysis of the literature significantly favored longer-term antimicrobial prophylaxis of more than 24 h in these patients^[72]. Similarly, Lador *et al.*^[73] showed that shorter duration of prophylaxis (≤ 24 h) was associated with a higher rate of DSWI, surgical intervention for any kind of SSI, and endocarditis; whereas, no difference between 48 h vs longer durations was found for all outcomes.

There is absolutely no data for continuing antimicrobial prophylaxis until chest drains are removed^[61]. Some studies highlighted the importance of weight-based antibiotic dosing in obese patients and the need for repeated doses during prolonged procedures (more than two half-lives of the drug) or in case of excessive blood loss during the procedure^[11,74]. Other investigators reported that a cefazolin bolus followed by continuous infusion improved pharmacokinetic and pharmacodynamic values, including concentrations in the cardiac muscle^[75].

MANAGEMENT

Debridement with primary closure has been the treatment of choice for a long time and, until now, it can be considered for infection localized to a small part of the sternum with little or no purulent drainage. Debridement is usually associated with the advancement of the pectoralis muscles and can be done in a single phase procedure or in a delayed closure with multiple open dressing changes followed by sternal re-wiring^[17,76-78]. The latter treatment allows improved accuracy in assessing the extent of the sternal infection and reduces the risk of recurrent infection but carries on major disadvantages: Thoracic instability, prolonged immobilization, and mechanical ventilation with increased risk of complications such as thrombosis, muscular weakness, and pneumonia^[17,76-79]. Concerns still remain about the need for obtaining negative cultures at the time of closure. Two recent studies found that the presence of positive tissue cultures did not affect the rate of recurrent infections^[80,81].

An important step forward in the treatment of DSWI occurred with the introduction of continuous irrigation using closed chest catheter following revision. Further developments were achieved with antibiotic irrigation but several studies have reported high rates of failure and mortality^[82-84].

The unsatisfactory results of these different approaches increased interest in plastic procedures as alternative treatments^[6,79,84]. Bilateral pectoralis muscle flaps, as either advancement or turnover flaps, are the most usual plastic procedures in the dealing of DSWI^[16,85]. This surgical management has a quite low mortality rate but carries a series of disadvantages, including

additional surgical trauma and late flap-related morbidity such as muscular weakness, pain, and hernias^[86]. An alternative plastic procedure to pectoralis muscle flaps is the use of omentum that promotes significant angiogenesis, immunologic function, and antimicrobial activity supporting tissue-generation promotion with great capacity to occupy dead space^[6,87,88]. Usually, the use of omentum is considered in the case of complex wounds or when the defect is extremely wide with significant sternal loss. Specifically, a definite preference has been expressed for the use of omentum when the primary causative pathogen is particularly resistant, such as MRSA^[80,89] and *Candida*^[90] or when the patients suffering from diabetes mellitus^[91].

However, complications occurred in up to 18% of patients treated with this approach^[16,92].

Several recent studies, meta-analyses, and systematic reviews have validated the efficacy of NPWT in DSWI either as a single-line therapy, or as a "bridge" prior to final surgical closure^[93-97]. This wound-healing technique is based on the application of continuous or intermittent negative pressure to a wound, which results in arteriolar dilatation and, subsequently, determines wound perfusion and granulation tissue proliferation^[57,85,93]. *In vitro* and clinical studies designed to determine the effect of NPWT lent convincing evidence of efficacy and safety in term of decrease of edema, exudation, and microbial colonization as well as reduction of inflammatory cytokine release^[57,85,98-100].

In case of diagnosis of DSWI, an early application of NPWT was associated to a faster healing and an increased likelihood of survival^[18,97,101,102]. Moreover, several studies demonstrated shorter treatment duration and length of hospital stay, as well as lower costs in patients treated with NPWT^[96,98,100,103]. NPWT was also successfully applied in the case of MRSA mediastinitis and as a temporizing treatment prior to secondary closure in mediastinitis due to *Candida*^[90,104,105].

Conversely, other authors suggested that prolonged application of NPWT can result in chronic infection due to a shift in bacterial species and to an increased growth of some of them, such as *Staphylococcus aureus*^[99,106]. Different studies have focused on factors that can predict failure of NPWT. Gdalevitch *et al.*^[107] found that positive blood cultures, wound depth of ≥ 4 cm, and high degree of bony exposure and sternal instability are significant predictors of NPWT failure. Pericleous *et al.*^[108] highlighted also the importance of lung emphysema, corticosteroids, and advanced age. Finally, Gustafsson *et al.*^[109] stressed bacteremia or elevated plasma C-reactive protein levels as the most sensitive predictors of failure.

The positive effects of NPWT on complicated surgical wounds have triggered the interest in using NPWT also after closure of clean and sutured wounds to prevent SSIs in patients at high risk of developing DSWI^[110]. The surgical incision management system (Prevena™ Incision Management System, Kinetic Concepts Inc., San Antonio, TX, United States) consists of a single-use NPWT that delivers negative pressure of 75-125 mmHg (10-16.7

KPa); this system holds the incision edges together, reduces lateral tension and edema, stimulates perfusion, and protects the surgical site from external infectious sources^[110]. Grauhan *et al.*^[111] showed significant reduction of SSIs in obese patients (body mass index > 30 kg/m²) with median sternotomy compared with patients treated with standard wound dressings. In general, retrospective studies and randomized controlled trials provided a substantial body of evidence that the use of this prophylactic wound dressing technique may reduce the incidence of wound infections^[112-114].

CONCLUSION

Despite several progresses in prevention and perioperative care, DSWI is still a permanent concern in cardiac surgery because of its significant rate and relevant impact on length of hospital stay, costs, and mortality. The incidence of this complication is in part due to the increased number of patients at high-risk for infection because of advanced age and rate of relevant comorbidities in the population undergoing cardiac surgery. A rigorous attention to the details of preoperative, intraoperative, and postoperative management could contribute to keep DSWIs at a minimal rate.

REFERENCES

- 1 Wang FD, Chang CH. Risk factors of deep sternal wound infections in coronary artery bypass graft surgery. *J Cardiovasc Surg* (Torino) 2000; **41**: 709-713 [PMID: 11149637]
- 2 Ridderstolpe L, Gill H, Granfeldt H, Ahlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. *Eur J Cardiothorac Surg* 2001; **20**: 1168-1175 [PMID: 11717023 DOI: 10.1016/S1010-7940(01)00991-5]
- 3 Lu JC, Grayson AD, Jha P, Srinivasan AK, Fabri BM. Risk factors for sternal wound infection and mid-term survival following coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2003; **23**: 943-949 [PMID: 12829070 DOI: 10.1016/S1010-7940(03)00137-4]
- 4 Abboud CS, Wey SB, Baltar VT. Risk factors for mediastinitis after cardiac surgery. *Ann Thorac Surg* 2004; **77**: 676-683 [PMID: 14759458 DOI: 10.1016/S0003-4975(03)01523-6]
- 5 Salehi Omran A, Karimi A, Ahmadi SH, Davoodi S, Marzban M, Movahedi N, Abbasi K, Boroumand MA, Davoodi S, Moshtaghi N. Superficial and deep sternal wound infection after more than 9000 coronary artery bypass graft (CABG): incidence, risk factors and mortality. *BMC Infect Dis* 2007; **7**: 112 [PMID: 17888179 DOI: 10.1186/1471-2334-7-112]
- 6 Filsofi F, Castillo JG, Rahmanian PB, Broumand SR, Silvey G, Carpentier A, Adams DH. Epidemiology of deep sternal wound infection in cardiac surgery. *J Cardiothorac Vasc Anesth* 2009; **23**: 488-494 [PMID: 19376733 DOI: 10.1053/j.jvca.2009.02.007]
- 7 Kanafani ZA, Arduino JM, Muhlbaier LH, Kaye KS, Allen KB, Carmeli Y, Corey GR, Cosgrove SE, Fraser TG, Harris AD, Karchmer AW, Lautenbach E, Rupp ME, Peterson ED, Straus WL, Fowler VG. Incidence of and preoperative risk factors for Staphylococcus aureus bacteremia and chest wound infection after cardiac surgery. *Infect Control Hosp Epidemiol* 2009; **30**: 242-248 [PMID: 19199534 DOI: 10.1086/596015]
- 8 Tom TS, Kruse MW, Reichman RT. Update: Methicillin-resistant Staphylococcus aureus screening and decolonization in cardiac surgery. *Ann Thorac Surg* 2009; **88**: 695-702 [PMID: 19632455 DOI: 10.1016/j.athoracsurg.2009.02.010]
- 9 Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011; **58**: e123-e210 [PMID: 22070836 DOI: 10.1016/j.jacc.2011.08.009]
- 10 Bryan CS, Yarbrough WM. Preventing deep wound infection after coronary artery bypass grafting: a review. *Tex Heart Inst J* 2013; **40**: 125-139 [PMID: 23678210]
- 11 Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis* 2006; **43**: 322-330 [PMID: 16804848 DOI: 10.1086/505220]
- 12 Karra R, McDermott L, Connelly S, Smith P, Sexton DJ, Kaye KS. Risk factors for 1-year mortality after postoperative mediastinitis. *J Thorac Cardiovasc Surg* 2006; **132**: 537-543 [PMID: 16935107 DOI: 10.1016/j.jtcvs.2006.04.037]
- 13 Graf K, Ott E, Vonberg RP, Kuehn C, Haverich A, Chaberny IF. Economic aspects of deep sternal wound infections. *Eur J Cardiothorac Surg* 2010; **37**: 893-896 [PMID: 19896860 DOI: 10.1016/j.ejcts.2009.10.005]
- 14 Braxton JH, Marrin CA, McGrath PD, Morton JR, Norotsky M, Charlesworth DC, Lahey SJ, Clough R, Ross CS, Olmstead EM, O'Connor GT. 10-year follow-up of patients with and without mediastinitis. *Semin Thorac Cardiovasc Surg* 2004; **16**: 70-76 [PMID: 15366690]
- 15 Ennker IC, Kojcici B, Ennker J, Vogt P, Melicherick J. [Examination of the opportunity costs and turnover situation in patients with deep sternal infections]. *Zentralbl Chir* 2012; **137**: 257-261 [PMID: 22194084 DOI: 10.1055/s-0031-1283762]
- 16 van Wingerden JJ, Lapid O, Boonstra PW, de Mol BA. Muscle flaps or omental flap in the management of deep sternal wound infection. *Interact Cardiovasc Thorac Surg* 2011; **13**: 179-187 [PMID: 21543366 DOI: 10.1510/icvts.2011.270652]
- 17 Izaddoost S, Withers EH. Sternal reconstruction with omental and pectoralis flaps: a review of 415 consecutive cases. *Ann Plast Surg* 2012; **69**: 296-300 [PMID: 22214791 DOI: 10.1097/SAP.0b013e31822af843]
- 18 Steingrimsson S, Gottfredsson M, Gudmundsdottir I, Sjögren J, Gudbjartsson T. Negative-pressure wound therapy for deep sternal wound infections reduces the rate of surgical interventions for early re-infections. *Interact Cardiovasc Thorac Surg* 2012; **15**: 406-410 [PMID: 22691377 DOI: 10.1093/icvts/ivs254]
- 19 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999; **27**: 97-132; quiz 133-134; discussion 96 [PMID: 10196487 DOI: 10.1016/S0196-6553(99)70088-X]
- 20 Dodds Ashley ES, Carroll DN, Engemann JJ, Harris AD, Fowler VG, Sexton DJ, Kaye KS. Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* 2004; **38**: 1555-1560 [PMID: 15156442 DOI: 10.1086/420819]
- 21 Harrington G, Russo P, Spelman D, Borrell S, Watson K, Barr W, Martin R, Edmonds D, Cocks J, Greenbough J, Lowe J, Randle L, Castell J, Browne E, Bellis K, Aberline M. Surgical-site infection rates and risk factor analysis in coronary artery bypass graft surgery. *Infect Control Hosp Epidemiol* 2004; **25**: 472-476 [PMID: 15242194]
- 22 Berrios-Torres SI, Mu Y, Edwards JR, Horan TC, Fridkin SK. Improved risk adjustment in public reporting: coronary artery bypass graft surgical site infections. *Infect Control Hosp Epidemiol* 2012; **33**: 463-469 [PMID: 22476272 DOI: 10.1086/665313]
- 23 Lepelletier D, Perron S, Bizouarn P, Caillon J, Drugeon H, Michaud JL, Duveau D. Surgical-site infection after cardiac surgery: incidence, microbiology, and risk factors. *Infect Control*

- Hosp Epidemiol* 2005; **26**: 466-472 [PMID: 15954485]
- 24 **Gummert JF**, Barten MJ, Hans C, Kluge M, Doll N, Walther T, Hentschel B, Schmitt DV, Mohr FW, Diegeler A. Mediastinitis and cardiac surgery--an updated risk factor analysis in 10,373 consecutive adult patients. *Thorac Cardiovasc Surg* 2002; **50**: 87-91 [PMID: 11981708 DOI: 10.1055/s-2002-26691]
 - 25 **Diez C**, Koch D, Kuss O, Silber RE, Friedrich I, Boergermann J. Risk factors for mediastinitis after cardiac surgery - a retrospective analysis of 1700 patients. *J Cardiothorac Surg* 2007; **2**: 23 [PMID: 17511885 DOI: 10.1186/1749-8090-2-23]
 - 26 **Fakih MG**, Sharma M, Khatib R, Berriel-Cass D, Meisner S, Harrington S, Saravolatz L. Increase in the rate of sternal surgical site infection after coronary artery bypass graft: a marker of higher severity of illness. *Infect Control Hosp Epidemiol* 2007; **28**: 655-660 [PMID: 17520536]
 - 27 **Robinson PJ**, Billah B, Leder K, Reid CM; ASCTS Database Committee. Factors associated with deep sternal wound infection and haemorrhage following cardiac surgery in Victoria. *Interact Cardiovasc Thorac Surg* 2007; **6**: 167-171 [PMID: 17669800 DOI: 10.1510/icvts.2006.143479]
 - 28 **Cayci C**, Russo M, Cheema FH, Martens T, Ozcan V, Argenziano M, Oz MC, Ascherman J. Risk analysis of deep sternal wound infections and their impact on long-term survival: a propensity analysis. *Ann Plast Surg* 2008; **61**: 294-301 [PMID: 18724131 DOI: 10.1097/SAP.0b013e31815acb6a]
 - 29 **Risnes I**, Abdelnoor M, Almdahl SM, Svennevig JL. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg* 2010; **89**: 1502-1509 [PMID: 20417768 DOI: 10.1016/j.athoracsur.2010.02.038]
 - 30 **Ogawa S**, Okawa Y, Sawada K, Goto Y, Yamamoto M, Koyama Y, Baba H, Suzuki T. Continuous postoperative insulin infusion reduces deep sternal wound infection in patients with diabetes undergoing coronary artery bypass grafting using bilateral internal mammary artery grafts: a propensity-matched analysis. *Eur J Cardiothorac Surg* 2015; Epub ahead of print [PMID: 25825261 DOI: 10.1093/ejcts/ezv106]
 - 31 **Gårdlund B**. Postoperative surgical site infections in cardiac surgery--an overview of preventive measures. *APMIS* 2007; **115**: 989-995 [PMID: 17931235 DOI: 10.1111/j.1600-0463.2007.00845.x]
 - 32 **von Eiff C**, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. *N Engl J Med* 2001; **344**: 11-16 [PMID: 11136954 DOI: 10.1056/NEJM200101043440102]
 - 33 **Walsh EE**, Greene L, Kirshner R. Sustained reduction in methicillin-resistant *Staphylococcus aureus* wound infections after cardiothoracic surgery. *Arch Intern Med* 2011; **171**: 68-73 [PMID: 20837818 DOI: 10.1001/archinternmed.2010.326]
 - 34 **Zhang L**, Garcia JM, Hill PC, Haile E, Light JA, Corso PJ. Cardiac surgery in renal transplant recipients: experience from Washington Hospital Center. *Ann Thorac Surg* 2006; **81**: 1379-1384 [PMID: 16564276 DOI: 10.1016/j.athoracsur.2005.10.045]
 - 35 **Sakamoto H**, Fukuda I, Oosaka M, Nakata H. Risk factors and treatment of deep sternal wound infection after cardiac operation. *Ann Thorac Cardiovasc Surg* 2003; **9**: 226-232 [PMID: 13129420]
 - 36 **Kramer R**, Groom R, Weldner D, Gallant P, Heyl B, Knapp R, Arnold A. Glycemic control and reduction of deep sternal wound infection rates: a multidisciplinary approach. *Arch Surg* 2008; **143**: 451-456 [PMID: 18490552 DOI: 10.1001/archsurg.143.5.451]
 - 37 **Rogers SO**, Zinner MJ. The role of perioperative hyperglycemia in postoperative infections. *Adv Surg* 2009; **43**: 103-109 [PMID: 19845172]
 - 38 **Gandhi GY**, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA, Schrader LM, Rizza RA, McMahon MM. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc* 2005; **80**: 862-866 [PMID: 16007890 DOI: 10.4065/80.7.862]
 - 39 **Brown JR**, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery -- the pre-intravenous insulin era. *Semin Thorac Cardiovasc Surg* 2006; **18**: 281-288 [PMID: 17395023 DOI: 10.1053/j.semtcvs.2006.04.004]
 - 40 **Møller AM**, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 2002; **359**: 114-117 [PMID: 11809253 DOI: 10.1016/S0140-6736(02)07369-5]
 - 41 **Engelman R**, Shahian D, Shemin R, Guy TS, Bratzler D, Edwards F, Jacobs M, Fernando H, Bridges C; Workforce on Evidence-Based Medicine, Society of Thoracic Surgeons. The Society of Thoracic Surgeons practice guideline series: Antibiotic prophylaxis in cardiac surgery, part II: Antibiotic choice. *Ann Thorac Surg* 2007; **83**: 1569-1576 [PMID: 17383396 DOI: 10.1016/j.athoracsur.2006.09.046]
 - 42 **Reiss S**, Pané-Farré J, Fuchs S, François P, Liebeke M, Schrenzel J, Lindequist U, Lalk M, Wolz C, Hecker M, Engelmann S. Global analysis of the *Staphylococcus aureus* response to mupirocin. *Antimicrob Agents Chemother* 2012; **56**: 787-804 [PMID: 22106209 DOI: 10.1128/AAC.05363-11]
 - 43 **Seah C**, Alexander DC, Louie L, Simor A, Low DE, Longtin J, Melano RG. MupB, a new high-level mupirocin resistance mechanism in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2012; **56**: 1916-1920 [PMID: 22252810 DOI: 10.1128/AAC.05325-11]
 - 44 **Tenover FC**, Tickler IA, Goering RV, Kreiswirth BN, Mediavilla JR, Persing DH; MRSA Consortium. Characterization of nasal and blood culture isolates of methicillin-resistant *Staphylococcus aureus* from patients in United States Hospitals. *Antimicrob Agents Chemother* 2012; **56**: 1324-1330 [PMID: 22155818 DOI: 10.1128/AAC.05804-11]
 - 45 **Kallen AJ**, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005; **26**: 916-922 [PMID: 16417031 DOI: 10.1086/505453]
 - 46 **Harbarth S**, Huttner B, Gervaz P, Fankhauser C, Chraïti MN, Schrenzel J, Licker M, Pittet D. Risk factors for methicillin-resistant *Staphylococcus aureus* surgical site infection. *Infect Control Hosp Epidemiol* 2008; **29**: 890-893 [PMID: 18785849 DOI: 10.1086/590193]
 - 47 **Zeitani J**, Penta de Peppo A, Moscarelli M, Guerrieri Wolf L, Scafuri A, Nardi P, Nanni F, Di Marzio E, De Vico P, Chiariello L. Influence of sternal size and inadvertent paramedian sternotomy on stability of the closure site: a clinical and mechanical study. *J Thorac Cardiovasc Surg* 2006; **132**: 38-42 [PMID: 16798300 DOI: 10.1016/j.jtcvs.2006.03.015]
 - 48 **Sreeram GM**, Welsby IJ, Sharma AD, Phillips-Bute B, Smith PK, Slaughter TF. Infectious complications after cardiac surgery: lack of association with fresh frozen plasma or platelet transfusions. *J Cardiothorac Vasc Anesth* 2005; **19**: 430-434 [PMID: 16085245 DOI: 10.1053/j.jvca.2005.05.001]
 - 49 **Banbury MK**, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. Transfusion increases the risk of postoperative infection after cardiovascular surgery. *J Am Coll Surg* 2006; **202**: 131-138 [PMID: 16377506 DOI: 10.1016/j.jamcollsurg.2005.08.028]
 - 50 **Peterson MD**, Borger MA, Rao V, Peniston CM, Feindel CM. Skeletonization of bilateral internal thoracic artery grafts lowers the risk of sternal infection in patients with diabetes. *J Thorac Cardiovasc Surg* 2003; **126**: 1314-1319 [PMID: 14666001 DOI: 10.1016/S0022-5223(03)00808-0]
 - 51 **Saso S**, James D, Vecht JA, Kidher E, Kokotsakis J, Malinowski V, Rao C, Darzi A, Anderson JR, Athanasiou T. Effect of skeletonization of the internal thoracic artery for coronary revascularization on the incidence of sternal wound infection. *Ann Thorac Surg* 2010; **89**: 661-670 [PMID: 20103378 DOI: 10.1016/j.athoracsur.2009.08.018]
 - 52 **Andreas M**, Zeitlinger M, Hoferl M, Jaeger W, Zimpfer D, Hiesmayr JM, Laufer G, Hutschala D. Internal mammary artery harvesting influences antibiotic penetration into presternal tissue. *Ann Thorac Surg* 2013; **95**: 1323-1329; discussion 1329-1330 [PMID: 23462262 DOI: 10.1016/j.athoracsur.2012.10.088]
 - 53 **Bhatti F**, Dunning J. Does liberal use of bone wax increase the risk

- of mediastinitis? *Interact Cardiovasc Thorac Surg* 2003; **2**: 410-412 [PMID: 17670085 DOI: 10.1016/S1569-9293(03)00180-4]
- 54 **Przyborowski J**, Hartrumpf M, Stock UA, Kuehnle RU, Albes JM. Is bonewax safe and does it help? *Ann Thorac Surg* 2008; **85**: 1002-1006 [PMID: 18291188 DOI: 10.1016/j.athoracsur.2007.10.036]
 - 55 **Anderson DJ**, Kaye KS, Classen D, Arias KM, Podgorny K, Burstin H, Calfee DP, Coffin SE, Dubberke ER, Fraser V, Gerding DN, Griffin FA, Gross P, Klompas M, Lo E, Marshall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, Saint S, Salgado CD, Weinstein RA, Wise R, Yokoe DS. Strategies to prevent surgical site infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008; **29** Suppl 1: S51-S61 [PMID: 18840089 DOI: 10.1086/591064]
 - 56 **Hidron AI**, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK; National Healthcare Safety Network Team; Participating National Healthcare Safety Network Facilities. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol* 2008; **29**: 996-1011 [PMID: 18947320 DOI: 10.1086/591861]
 - 57 **Sjögren J**, Malmström M, Gustafsson R, Ingemansson R. Post-sternotomy mediastinitis: a review of conventional surgical treatments, vacuum-assisted closure therapy and presentation of the Lund University Hospital mediastinitis algorithm. *Eur J Cardiothorac Surg* 2006; **30**: 898-905 [PMID: 17056269 DOI: 10.1016/j.ejcts.2006.09.020]
 - 58 **National Nosocomial Infections Surveillance System**. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; **32**: 470-485 [PMID: 15573054 DOI: 10.1016/j.ajic.2004.10.001]
 - 59 **Kreter B**, Woods M. Antibiotic prophylaxis for cardiothoracic operations. Meta-analysis of thirty years of clinical trials. *J Thorac Cardiovasc Surg* 1992; **104**: 590-599 [PMID: 1387437]
 - 60 **Spellberg B**, Blaser M, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, Gerding D, Lynfield R, Reller LB, Rex J, Schwartz D, Septimus E, Tenover FC, Gilbert DN. Combating antimicrobial resistance: policy recommendations to save lives. *Clin Infect Dis* 2011; **52** Suppl 5: S397-S428 [PMID: 21474585 DOI: 10.1093/cid/cir153]
 - 61 **Edwards FH**, Engelman RM, Houck P, Shahian DM, Bridges CR. The Society of Thoracic Surgeons Practice Guideline Series: Antibiotic Prophylaxis in Cardiac Surgery, Part I: Duration. *Ann Thorac Surg* 2006; **81**: 397-404 [PMID: 16368422 DOI: 10.1016/j.athoracsur.2005.06.034]
 - 62 **Curtis JJ**, Boley TM, Walls JT, Hamory B, Schmaltz RA. Randomized, prospective comparison of first- and second-generation cephalosporins as infection prophylaxis for cardiac surgery. *Am J Surg* 1993; **166**: 734-737 [PMID: 8273859]
 - 63 **Galbraith U**, Schilling J, von Segesser LK, Carrel T, Turina M, Geroulanos S. Antibiotic prophylaxis in cardiovascular surgery: a prospective randomized comparative trial of one day cefazolin versus single dose cefuroxime. *Drugs Exp Clin Res* 1993; **19**: 229-234 [PMID: 8174496]
 - 64 **Townsend TR**, Reitz BA, Bilker WB, Bartlett JG. Clinical trial of cefamandole, cefazolin, and cefuroxime for antibiotic prophylaxis in cardiac operations. *J Thorac Cardiovasc Surg* 1993; **106**: 664-670 [PMID: 8412261]
 - 65 **Cotogni P**, Passera R, Barbero C, Gariboldi A, Moscato D, Izzo G, Rinaldi M. Intraoperative vancomycin pharmacokinetics in cardiac surgery with or without cardiopulmonary bypass. *Ann Pharmacother* 2013; **47**: 455-463 [PMID: 23512663 DOI: 10.1345/aph.1R669]
 - 66 **Bolon MK**, Morlote M, Weber SG, Koplan B, Carmeli Y, Wright SB. Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: a meta-analysis. *Clin Infect Dis* 2004; **38**: 1357-1363 [PMID: 15156470 DOI: 10.1086/383318]
 - 67 **Classen DC**, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992; **326**: 281-286 [PMID: 1728731 DOI: 10.1056/NEJM199201303260501]
 - 68 **Weber WP**, Marti WR, Zwahlen M, Misteli H, Rosenthal R, Reck S, Fueglistaler P, Bolli M, Trampuz A, Oertli D, Widmer AF. The timing of surgical antimicrobial prophylaxis. *Ann Surg* 2008; **247**: 918-926 [PMID: 18520217 DOI: 10.1097/SLA.0b013e31816c3fec]
 - 69 **Steinberg JP**, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, Dellinger EP, Burke JP, Simmons B, Kritchevsky SB; Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) Study Group. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg* 2009; **250**: 10-16 [PMID: 19561486 DOI: 10.1097/SLA.0b013e3181ad5fca]
 - 70 **Hawn MT**, Richman JS, Vick CC, Deierhoi RJ, Graham LA, Henderson WG, Itani KM. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. *JAMA Surg* 2013; **148**: 649-657 [PMID: 23552769 DOI: 10.1001/jamasurg.2013.134]
 - 71 **Bratzler DW**, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; **38**: 1706-1715 [PMID: 15227616 DOI: 10.1086/421095]
 - 72 **Mertz D**, Johnstone J, Loeb M. Does duration of perioperative antibiotic prophylaxis matter in cardiac surgery? A systematic review and meta-analysis. *Ann Surg* 2011; **254**: 48-54 [PMID: 21412147 DOI: 10.1097/SLA.0b013e318214b7e4]
 - 73 **Lador A**, Nasir H, Mansur N, Sharoni E, Biderman P, Leibovici L, Paul M. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. *J Antimicrob Chemother* 2012; **67**: 541-550 [PMID: 22083832 DOI: 10.1093/jac/dkr470]
 - 74 **Caffarelli AD**, Holden JP, Baron EJ, Lemmens HJ, D'Souza H, Yau V, Olcott C, Reitz BA, Miller DC, van der Starre PJ. Plasma cefazolin levels during cardiovascular surgery: effects of cardiopulmonary bypass and profound hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 2006; **131**: 1338-1343 [PMID: 16733167 DOI: 10.1016/j.jtcvs.2005.11.047]
 - 75 **Adembri C**, Ristori R, Chelazzi C, Arrigucci S, Cassetta MI, De Gaudio AR, Novelli A. Cefazolin bolus and continuous administration for elective cardiac surgery: improved pharmacokinetic and pharmacodynamic parameters. *J Thorac Cardiovasc Surg* 2010; **140**: 471-475 [PMID: 20570290 DOI: 10.1016/j.jtcvs.2010.03.038]
 - 76 **Schroeyers P**, Wellens F, Degrieck I, De Geest R, Van Praet F, Vermeulen Y, Vanermen H. Aggressive primary treatment for poststernotomy acute mediastinitis: our experience with omental- and muscle flaps surgery. *Eur J Cardiothorac Surg* 2001; **20**: 743-746 [PMID: 11574218 DOI: 10.1016/S1010-7940(01)00873-9]
 - 77 **Fleck TM**, Koller R, Giovanoli P, Moidl R, Czerny M, Fleck M, Wolner E, Grabenwoger M. Primary or delayed closure for the treatment of poststernotomy wound infections? *Ann Plast Surg* 2004; **52**: 310-314 [PMID: 15156988]
 - 78 **Wong CH**, Senewiratne S, Garlick B, Mullany D. Two-stage management of sternal wound infection using bilateral pectoralis major advancement flap. *Eur J Cardiothorac Surg* 2006; **30**: 148-152 [PMID: 16725333 DOI: 10.1016/j.ejcts.2006.03.049]
 - 79 **Jones G**, Jurkiewicz MJ, Bostwick J, Wood R, Bried JT, Culbertson J, Howell R, Eaves F, Carlson G, Nahai F. Management of the infected median sternotomy wound with muscle flaps. The Emory 20-year experience. *Ann Surg* 1997; **225**: 766-776; discussion 776-778 [PMID: 9230817]
 - 80 **Danner BC**, Zenker D, Didilis VN, Grossmann M, Stojanovic T, Seipelt R, Tirilomis T, Schöndube FA. Transposition of greater omentum in deep sternal wound infection caused by methicillin-resistant Staphylococci, with differing clinical course for MRSA and MRSE. *Thorac Cardiovasc Surg* 2011; **59**: 21-24 [PMID: 21243567 DOI: 10.1055/s-0030-1250373]
 - 81 **Rodriguez Cetina Bieffer H**, Sündermann SH, Emmert MY, Rancic Z, Salzberg SP, Grünfelder J, Falk V, Plass AR. Negative microbiological results are not mandatory in deep sternal wound

- infections before wound closure. *Eur J Cardiothorac Surg* 2012; **42**: 306-310; discussion 310 [PMID: 22290924 DOI: 10.1093/ejcts/ejz326]
- 82 Calvat S, Trouillet JL, Nataf P, Vuagnat A, Chastre J, Gibert C. Closed drainage using Redon catheters for local treatment of poststernotomy mediastinitis. *Ann Thorac Surg* 1996; **61**: 195-201 [PMID: 8561552 DOI: 10.1016/0003-4975(95)00921-3]
 - 83 Rand RP, Cochran RP, Aziz S, Hofer BO, Allen MD, Verrier ED, Kunzelman KS. Prospective trial of catheter irrigation and muscle flaps for sternal wound infection. *Ann Thorac Surg* 1998; **65**: 1046-1049 [PMID: 9564925 DOI: 10.1016/S0003-4975(98)00087-3]
 - 84 Catarino PA, Chamberlain MH, Wright NC, Black E, Campbell K, Robson D, Pillai RG. High-pressure suction drainage via a polyurethane foam in the management of poststernotomy mediastinitis. *Ann Thorac Surg* 2000; **70**: 1891-1895 [PMID: 11156090 DOI: 10.1016/S0003-4975(00)02173-1]
 - 85 Ennker IC, Pietrowski D, Vöhringer L, Kojcici B, Albert A, Vogt PM, Ennker J. Surgical debridement, vacuum therapy and pectoralis plasty in poststernotomy mediastinitis. *J Plast Reconstr Aesthet Surg* 2009; **62**: 1479-1483 [PMID: 18996074 DOI: 10.1016/j.bjps.2008.05.017]
 - 86 Pairolero PC, Arnold PG, Harris JB. Long-term results of pectoralis major muscle transposition for infected sternotomy wounds. *Ann Surg* 1991; **213**: 583-589; discussion 589-590 [PMID: 2039289 DOI: 10.1097/0000658-199106000-00008]
 - 87 De Brabandere K, Jacobs-Tulleneers-Thevissen D, Czapla J, La Meir M, Delvaux G, Wellens F. Negative-pressure wound therapy and laparoscopic omentoplasty for deep sternal wound infections after median sternotomy. *Tex Heart Inst J* 2012; **39**: 367-371 [PMID: 22719146]
 - 88 Vyas RM, Prsic A, Orgill DP. Transdiaphragmatic omental harvest: a simple, efficient method for sternal wound coverage. *Plast Reconstr Surg* 2013; **131**: 544-552 [PMID: 23142938 DOI: 10.1097/PRS.0b013e31827c6e2e]
 - 89 Hirata N, Hatsuoka S, Amemiya A, Ueno T, Kosakai Y. New strategy for treatment of MRSA mediastinitis: one-stage procedure for omental transposition and closed irrigation. *Ann Thorac Surg* 2003; **76**: 2104-2106 [PMID: 14667661 DOI: 10.1016/S0003-4975(03)00744-6]
 - 90 Osada H, Nakajima H, Morishima M, Su T. Candidal mediastinitis successfully treated using vacuum-assisted closure following open-heart surgery. *Interact Cardiovasc Thorac Surg* 2012; **14**: 872-874 [PMID: 22422875 DOI: 10.1093/icvts/ivs084]
 - 91 Stump A, Bedri M, Goldberg NH, Slezak S, Silverman RP. Omental transposition flap for sternal wound reconstruction in diabetic patients. *Ann Plast Surg* 2010; **65**: 206-210 [PMID: 20606588 DOI: 10.1097/SAP.0b013e3181c9c31a]
 - 92 Schols RM, Lauwers TM, Geskes GG, van der Hulst RR. Deep sternal wound infection after open heart surgery: current treatment insights. A retrospective study of 36 cases. *Eur J Plast Surg* 2011; **34**: 487-492 [PMID: 22162911 DOI: 10.1007/s00238-011-0573-2]
 - 93 Fleck TM, Fleck M, Moidl R, Czerny M, Koller R, Giovanoli P, Hiesmayer MJ, Zimpfer D, Wolner E, Grabenwoger M. The vacuum-assisted closure system for the treatment of deep sternal wound infections after cardiac surgery. *Ann Thorac Surg* 2002; **74**: 1596-1600; discussion 1600 [PMID: 12440614]
 - 94 Immer FF, Durrer M, Mühlemann KS, Erni D, Gahl B, Carrel TP. Deep sternal wound infection after cardiac surgery: modality of treatment and outcome. *Ann Thorac Surg* 2005; **80**: 957-961 [PMID: 16122463 DOI: 10.1016/j.athoracsur.2005.03.035]
 - 95 Raja SG, Berg GA. Should vacuum-assisted closure therapy be routinely used for management of deep sternal wound infection after cardiac surgery? *Interact Cardiovasc Thorac Surg* 2007; **6**: 523-527 [PMID: 17669926 DOI: 10.1510/icvts.2007.157370]
 - 96 Damiani G, Pinnarelli L, Sommella L, Tocco MP, Marvulli M, Magrini P, Ricciardi W. Vacuum-assisted closure therapy for patients with infected sternal wounds: a meta-analysis of current evidence. *J Plast Reconstr Aesthet Surg* 2011; **64**: 1119-1123 [PMID: 21256819 DOI: 10.1016/j.bjps.2010.11.022]
 - 97 Falagas ME, Tansarli GS, Kapaskelis A, Vardakas KZ. Impact of vacuum-assisted closure (VAC) therapy on clinical outcomes of patients with sternal wound infections: a meta-analysis of non-randomized studies. *PLoS One* 2013; **8**: e64741 [PMID: 23741379 DOI: 10.1371/journal.pone.0064741]
 - 98 Fuchs U, Zittermann A, Stuetgen B, Groening A, Minami K, Koerfer R. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: a retrospective analysis. *Ann Thorac Surg* 2005; **79**: 526-531 [PMID: 15680828 DOI: 10.1016/j.athoracsur.2004.08.032]
 - 99 Bapat V, El-Muttardi N, Young C, Venn G, Roxburgh J. Experience with Vacuum-assisted closure of sternal wound infections following cardiac surgery and evaluation of chronic complications associated with its use. *J Card Surg* 2008; **23**: 227-233 [PMID: 18435637 DOI: 10.1111/j.1540-8191.2008.00595.x]
 - 100 Vos RJ, Yilmaz A, Sonker U, Kelder JC, Kloppenburg GT. Vacuum-assisted closure of post-sternotomy mediastinitis as compared to open packing. *Interact Cardiovasc Thorac Surg* 2012; **14**: 17-21 [PMID: 22108946 DOI: 10.1093/icvts/ivr049]
 - 101 Petzina R, Hoffmann J, Navasardyan A, Malmsjö M, Stamm C, Unbehau A, Hetzer R. Negative pressure wound therapy for post-sternotomy mediastinitis reduces mortality rate and sternal re-infection rate compared to conventional treatment. *Eur J Cardiothorac Surg* 2010; **38**: 110-113 [PMID: 20171898 DOI: 10.1016/j.ejcts.2010.01.028]
 - 102 Assmann A, Boeken U, Feindt P, Schurr P, Akhyari P, Lichtenberg A. Vacuum-assisted wound closure is superior to primary rewiring in patients with deep sternal wound infection. *Thorac Cardiovasc Surg* 2011; **59**: 25-29 [PMID: 21243568 DOI: 10.1055/s-0030-1250598]
 - 103 Yu AW, Rippel RA, Smock E, Jarral OA. In patients with post-sternotomy mediastinitis is vacuum-assisted closure superior to conventional therapy? *Interact Cardiovasc Thorac Surg* 2013; **17**: 861-865 [PMID: 23912622 DOI: 10.1093/icvts/ivt326]
 - 104 Modrau IS, Ejlersen T, Rasmussen BS. Emerging role of Candida in deep sternal wound infection. *Ann Thorac Surg* 2009; **88**: 1905-1909 [PMID: 19932259 DOI: 10.1016/j.athoracsur.2009.08.012]
 - 105 Morisaki A, Hosono M, Sasaki Y, Hirai H, Sakaguchi M, Nakahira A, Seo H, Suehiro S, Shibata T. Evaluation of risk factors for hospital mortality and current treatment for poststernotomy mediastinitis. *Gen Thorac Cardiovasc Surg* 2011; **59**: 261-267 [PMID: 21484552 DOI: 10.1007/s11748-010-0727-3]
 - 106 Gaudreau G, Costache V, Houde C, Cloutier D, Montalin L, Voisine P, Baillot R. Recurrent sternal infection following treatment with negative pressure wound therapy and titanium transverse plate fixation. *Eur J Cardiothorac Surg* 2010; **37**: 888-892 [PMID: 19775906 DOI: 10.1016/j.ejcts.2009.07.043]
 - 107 Gdalevitch P, Afilalo J, Lee C. Predictors of vacuum-assisted closure failure of sternotomy wounds. *J Plast Reconstr Aesthet Surg* 2010; **63**: 180-183 [PMID: 19028156 DOI: 10.1016/j.bjps.2008.08.020]
 - 108 Pericleous A, Dimitrakakis G, Photiades R, von Oppell UO. Assessment of vacuum-assisted closure therapy on the wound healing process in cardiac surgery. *Int Wound J* 2015; Epub ahead of print [PMID: 25728664 DOI: 10.1111/iwjl.12430]
 - 109 Gustafsson R, Johnsson P, Algotsson L, Blomquist S, Ingemansson R. Vacuum-assisted closure therapy guided by C-reactive protein level in patients with deep sternal wound infection. *J Thorac Cardiovasc Surg* 2002; **123**: 895-900 [PMID: 12019374 DOI: 10.1067/mtc.2002.121306]
 - 110 Dohmen PM, Misfeld M, Borger MA, Mohr FW. Closed incision management with negative pressure wound therapy. *Expert Rev Med Devices* 2014; **11**: 395-402 [PMID: 24754343 DOI: 10.1586/17434440.2014.911081]
 - 111 Grauhan O, Navasardyan A, Hofmann M, Müller P, Stein J, Hetzer R. Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy. *J Thorac Cardiovasc Surg* 2013; **145**: 1387-1392 [PMID: 23111014 DOI: 10.1016/j.jtcvs.2012.09.040]

- 112 **Atkins BZ**, Wooten MK, Kistler J, Hurley K, Hughes GC, Wolfe WG. Does negative pressure wound therapy have a role in preventing poststernotomy wound complications? *Surg Innov* 2009; **16**: 140-146 [PMID: 19460818 DOI: 10.1177/1553350609334821]
- 113 **Colli A**, Camara ML. First experience with a new negative pressure incision management system on surgical incisions after cardiac surgery in high risk patients. *J Cardiothorac Surg* 2011; **6**: 160 [PMID: 22145641 DOI: 10.1186/1749-8090-6-160]
- 114 **Grauhan O**, Navasardyan A, Tutkun B, Hennig F, Müller P, Hummel M, Hetzer R. Effect of surgical incision management on wound infections in a poststernotomy patient population. *Int Wound J* 2014; **11** Suppl 1: 6-9 [PMID: 24851729 DOI: 10.1111/iwj.12294]

P- Reviewer: Yao YM **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Liu SQ



Why there is a need to discuss pulmonary hypertension other than pulmonary arterial hypertension?

Athanasios Papathanasiou, George Nakos

Athanasios Papathanasiou, George Nakos, Intensive Care Unit, University Hospital of Ioannina, 45500 Ioannina, Greece

Author contributions: Both authors contributed equally to this editorial.

Conflict-of-interest statement: George Nakos declares no conflict of interest related to this publication. Athanasios Papathanasiou declares no conflict of interest related to this publication.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: George Nakos, MD, PhD, DTM, FCCP, Professor, Intensive Care Unit, University Hospital of Ioannina, PO Box 1186, 45500 Ioannina, Greece. gnakos@cc.uoi.gr
Telephone: +30-26-51099279
Fax: +30-26-51099353

Received: May 25, 2015
Peer-review started: May 26, 2015
First decision: July 10, 2015
Revised: August 11, 2015
Accepted: September 10, 2015
Article in press: September 16, 2015
Published online: November 4, 2015

Abstract

Pulmonary hypertension (PH) is a condition characterized by the elevation of the mean pulmonary artery pressure above 25 mmHg and the pulmonary vascular resistance above 3 wood units. Pulmonary arterial hypertension (PAH) is an uncommon condition

with severe morbidity and mortality, needing early recognition and appropriate and specific treatment. PH is frequently associated with hypoxemia, mainly chronic obstructive pulmonary disease and DPLD and/or left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Although in the majority of patients with PH the cause is not PAH, a significant number of published studies are still in regard to group I PH, leading to a logical assumption that PH due to other causes is not such an important issue. So, is there a reason to discuss PH other than PAH? Chronic lung diseases, mainly chronic obstructive lung disease and DPLD, are associated with a high incidence of PH which is linked to exercise limitations and a worse prognosis. Although pathophysiological studies suggest that specific PAH therapy may benefit such patients, the results presented from small studies in regard to the safety and effectiveness of the specific PAH therapy are discouraging. PH is a common complication of left heart disease and is related to disease severity, especially in patients with reduced ejection fraction. There are two types of PH related to LHD based on diastolic pressure difference (DPD, defined as diastolic pulmonary artery pressure - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH, defined as PAWP > 15 mmHg and DPD ≥ 7 mmHg. The potential use of PAH therapies in patients with PH related to left heart disease is based on a logical pathobiological rationale. In patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation. Unfortunately, so far, there is no evidence supporting the use of specific PAH therapies in patients with PH related to left heart disease. In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease, affecting the outcome and quality of life. The disappointing results regarding the effectiveness of specific PAH therapies in patients with

chronic lung diseases and LHD underline the need for seeking new underlying mechanisms and thus novel therapies targeting PH due to left heart disease and/or lung diseases.

Key words: Pulmonary hypertension; Pulmonary arterial hypertension; Chronic obstructive pulmonary disease; Heart failure; Treatment

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pulmonary arterial hypertension (PAH) is a rare disease that concerns a small population of patients. Recently, there has been a significant number of research, publications and novel therapies concerning PAH. However, pulmonary hypertension (PH), that concerns a much larger population of patients with common diseases such as lung and left heart diseases (LHD), is generally overlooked despite the fact that it significantly affects the prognosis of these patients. This editorial underlines the need for further research in regard to the pathogenesis and novel therapies for PH related to lung and LHD.

Papathanasiou A, Nakos G. Why there is a need to discuss pulmonary hypertension other than pulmonary arterial hypertension? *World J Crit Care Med* 2015; 4(4): 274-277 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i4/274.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i4.274>

TEXT

Pulmonary hypertension (PH) is a condition characterized by the elevation of mean pulmonary artery pressure (mPAP) above 25 mmHg and pulmonary vascular resistance (PVR) above 3 wood units^[1]. Pulmonary arterial hypertension (PAH), *i.e.*, group I according to the latest international guidelines^[2], is a rather uncommon condition requiring specific treatment. In the majority of patients with PH, elevated pressures in pulmonary circulation are due to hypoxemia, mainly chronic obstructive pulmonary disease (COPD) and diffuse parenchymal lung diseases (DPLD including idiopathic pulmonary fibrosis and sarcoidosis), and/or due to left heart diseases (LHD), mainly heart failure with reduced or preserved ejection fraction. Furthermore, a small proportion of PH is due to chronic thromboembolic disease and other conditions. Definitions of the above mentioned subgroups of patients with PH are shown in Table 1.

Group I PH, *i.e.*, PAH, is either familial, idiopathic or is associated with various well specified diseases^[1]. In recent years, a large number of studies have shed light on the underlying pathophysiologic mechanisms for the development of PAH, eventually leading to targeted therapies that improved the morbidity and survival of these patients. Currently, there are three

known pathways that play a part in cell proliferation and vasoconstriction in the pulmonary arteries of patients with PAH^[3]. Treatments for PAH are aimed at these pathways^[4]. The first one is the prostacyclin pathway. Prostacyclin is a potent vasodilator and drugs called epoprostanoids, *i.e.*, epoprostenol, treprostinil and iloprost, targeting this pathway, aim to increase the level of prostacyclin in the body. The second pathway is the endothelin pathway. Endothelin is a known potent vasoconstrictor. The class of drugs that targets this pathway is called endothelin receptor antagonist, *i.e.*, bosentan, macitentan and ambrisentan. These drugs block the A and B endothelin receptors in the blood vessels from responding to endothelin. Finally, the third pathway is the nitric oxide pathway. Nitric oxide is a potent vasodilator. There are two classes of medications that target this pathway. Phosphodiesterase type 5 is a molecule in the body that interrupts the production of nitric oxide. The drugs that target this pathway are called phosphodiesterase type 5 inhibitors. Soluble guanylate cyclase stimulators work by stimulating an enzyme inside the cells called soluble guanylate cyclase. By increasing the activity of this enzyme, there is an increase in the production of cyclic GMP, which in turn leads to relaxation of the pulmonary arteries and improvements in PH. Currently, two phosphodiesterase type 5 inhibitors, sildenafil and tadalafil, and one soluble guanylate cyclase stimulator, riociguat, have been approved^[4].

The majority of published studies concern PAH, thus leading to a logical assumption that PH due to other causes is not such an important issue. This is also enforced by the fact that published guidelines regarding PH groups II, III and IV cover only 26 out of 126 pages. So, is there a reason to discuss PH other than PAH?

COPD and DPLD, including idiopathic pulmonary fibrosis and sarcoidosis, are associated with a high incidence of PH, which is linked to exercise limitations and a worse prognosis^[5]. Data showed that the prevalence of PH in COPD patients depends on the severity of the disease and the definition of PH. Accumulating data suggests that in approximately 90% of patients with severe disease, mPAP was more than 20 mmHg, with most ranging between 20 and 35 mmHg while 3% to 5% of the patients demonstrated "severe PH", *i.e.*, mPAP > 35 to 40 mmHg^[6]. The "severe PH group" includes only a minority of chronic lung disease patients suspected of having significant vascular abnormalities (remodelling) accompanying the parenchymal disease^[7]. For COPD, this corresponds to approximately 1% of the entire population^[6].

Chronic hypoxia and fibroproliferation in DPLD lead to the remodelling of both the pulmonary arterial vascular wall and the pulmonary parenchyma due to common pathophysiological ways, while new data indicate that pathogenetic concepts that primarily relate to idiopathic pulmonary fibrosis may also take place in other forms of pulmonary fibrosis, including connective tissue diseases

Table 1 The definitions of pulmonary hypertension groups I, II, III, IV^[1,7,22]

Group	Definition
Group I: Pulmonary arterial hypertension	Is defined as: Mean pulmonary artery pressure ≥ 25 mmHg at rest, and end-expiratory pulmonary artery wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance > 3 Wood units
Group II: PH due to left heart disease	Is defined as: mPAP ≥ 25 mmHg, and PAWP > 15 mmHg, and normal or reduced CO
Group III: PH due to chronic lung disease and/or hypoxia	Patients with confirmed COPD or DPLD, without chronic thromboembolic disease or left heart disease, who meet at least two of the following criteria: mPAP > 35 mmHg mPAP ≥ 25 mmHg AND cardiac index < 2 lt/min per square pulmonary vascular resistance > 6 Wood units
Group IV: Chronic thromboembolic pulmonary hypertension	CTEPH is defined as pre-capillary PH as assessed by right heart catheterization (mean PAP ≥ 25 mmHg, PCWP ≤ 15 mmHg) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least three months of effective anticoagulation

PH: Pulmonary hypertension; CO: Cardiac output; COPD: Chronic obstructive pulmonary disease; DPLD: Diffuse parenchymal lung diseases; PAP: Pulmonary artery pressure.

and granulomatous diseases such as sarcoidosis^[8]. This leads to a rationale for evaluating the safety and effectiveness of the specific PAH therapy in such patients^[5]. Data from such trials are discouraging. In COPD, pulmonary vasodilation without deterioration of gas exchange is more challenging than in lung fibrosis caused by the presence of low ventilation/perfusion ratio areas. Inhaled prostanoids may acutely reduce mPAP and PVR while largely maintaining gas exchange in COPD patients with PH^[9].

However, long-term clinical trials have not been reported. In COPD patients with mild PH, bosentan, a nonselective endothelin-1 receptor antagonist, caused deterioration of gas exchange with a lack of improvement in peak oxygen uptake, exercise capacity and quality of life in a small randomized controlled trial^[10]. On the other hand, another small trial reported an improvement in exercise capacity upon treatment of COPD patients with PH with bosentan^[11].

Robust data on the effect of endothelin receptors antagonists on pulmonary hemodynamics and exercise tolerance in COPD patients are lacking^[5].

PH is a common complication of LHD^[12]. The presence of PH is often considered as a symptom of the underlying condition and often related to disease severity, especially in patients with reduced ejection fraction of the left ventricle^[13]. The current hemodynamic definition of PH related to LHD combines a mPAP ≥ 25 mmHg, a pulmonary artery wedge pressure (PAWP) > 15 mmHg and a normal or reduced cardiac output. There are also two types of PH related to LHD based on the diastolic pressure difference (DPD, defined as diastolic PAP - mean PAWP): Isolated post-capillary PH, defined as PAWP > 15 mmHg and DPD < 7 mmHg, and combined post-capillary PH and pre-capillary PH defined as PAWP > 15 mmHg and DPD ≥ 7 mmHg^[13].

The potential use of PAH therapies in patients with PH related to LHD is based on a logical pathobiological rationale, while in patients with heart failure, endothelial dysfunction has been proposed as a cause of PH and hence as a target for treatment, supported by the presence of increased endothelin-1 activity and impaired nitric oxide-dependent vasodilation^[14]. Unfortunately, so far, there is no evidence supporting the use of specific

PAH therapies in patients with PH related to LHD^[13]. It must be pointed out that there are fundamental differences in the pathophysiologic pathways between patients with heart failure with reduced and preserved ejection fraction. These differences suggest that more pathophysiologically targeted drugs and therapies are needed for each case^[15].

Therefore, it is anticipated that PAH therapies might have a different effect in patients with heart failure and preserved ejection fraction compared with other forms of heart failure. Data on the use of PAH therapies in the context of heart failure and reduced or preserved ejection fraction with or without PH are scarce; with sildenafil and riociguat the most studied medications in this setting^[16-18].

Finally, specific PAH therapies may have a place in the treatment of acute PH. In one of our studies, we showed that the postoperative co-administration of inhaled nitric oxide and oral sildenafil, a phosphodiesterase-5 inhibitor, in patients with out-of-proportion PH undergoing cardiac surgery is safe and results in an additive favourable effect on pulmonary arterial pressure and PVR, without systemic hypotension and ventilation/perfusion mismatch^[19].

Finally, left heart disease is a well-known but often underdiagnosed co-morbidity of COPD^[20,21]. The presence of left heart disease in COPD patients may additionally contribute to the pathogenesis and severity of PH and thus the cause of moderate to severe PH in patients with COPD may be the result of multiple causal factors. Data regarding the incidence of HF in COPD patients are accumulating, but there is little known about the contribution of each condition to the presence and severity of PH in such patients.

In conclusion, the presence of PH in patients with conditions other than PAH contributes to the severity of the disease affecting the outcome and quality of life. Although these conditions affect a large proportion of patients with common diseases such as LHD and COPD/DPLD, there is a lack of data, pathophysiologic studies, and multicentre randomised trials addressing a target therapy for PH in such populations. The disappointing results for the effectiveness of specific PAH therapies in such populations underline the need to seek new

underlying mechanisms and thus novel therapies targeting PH due to LHD and/or lung diseases.

REFERENCES

- 1 **Hoeper MM**, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**: D42-D50 [PMID: 24355641 DOI: 10.1016/j.jacc.2013.10.032]
- 2 **Simonneau G**, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**: D34-D41 [PMID: 24355639 DOI: 10.1016/j.jacc.2013.10.029]
- 3 **Humbert M**, Ghofrani HA. The molecular targets of approved treatments for pulmonary arterial hypertension. *Thorax* 2015; Epub ahead of print [PMID: 26219978 DOI: 10.1136/thoraxjnl-2015-207170]
- 4 **Humbert M**, Lau EM, Montani D, Jaïs X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation* 2014; **130**: 2189-2208 [PMID: 25602947 DOI: 10.1161/CIRCULATIONAHA.114.006974]
- 5 **Seeger W**, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry JL. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013; **62**: D109-D116 [PMID: 24355635 DOI: 10.1016/j.jacc.2013.10.036]
- 6 **Chaouat A**, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducoloné A, Ehrhart M, Kessler R, Weitzenblum E. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; **172**: 189-194 [PMID: 15831842 DOI: 10.1164/rccm.200401-006OC]
- 7 **Hoeper MM**, Andreas S, Bastian A, Claussen M, Ghofrani HA, Gorenflo M, Grohé C, Günther A, Halank M, Hammerl P, Held M, Krüger S, Lange TJ, Reichenberger F, Sablotzki A, Staehler G, Stark W, Wirtz H, Witt C, Behr J. Pulmonary hypertension due to chronic lung disease: updated Recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011; **154** Suppl 1: S45-S53 [PMID: 22221973 DOI: 10.1016/S0167-5273(11)70492-2]
- 8 **Behr J**, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J* 2008; **31**: 1357-1367 [PMID: 18515559 DOI: 10.1183/09031936.00171307]
- 9 **Blanco I**, Ribas J, Xaubet A, Gómez FP, Roca J, Rodríguez-Roisin R, Barberà JA. Effects of inhaled nitric oxide at rest and during exercise in idiopathic pulmonary fibrosis. *J Appl Physiol* (1985) 2011; **110**: 638-645 [PMID: 21183625 DOI: 10.1152/japplphysiol.01104.2010]
- 10 **Blanco I**, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodríguez-Roisin R, Roca J, Barberà JA. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2010; **181**: 270-278 [PMID: 19875684 DOI: 10.1164/rccm.200907-0988OC]
- 11 **Valerio G**, Bracciale P, Grazia D'Agostino A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2009; **3**: 15-21 [PMID: 19293199 DOI: 10.1177/1753465808103499]
- 12 **Bursi F**, McNallan SM, Redfield MM, Nkomo VT, Lam CS, Weston SA, Jiang R, Roger VL. Pulmonary pressures and death in heart failure: a community study. *J Am Coll Cardiol* 2012; **59**: 222-231 [PMID: 22240126 DOI: 10.1016/j.jacc.2011.06.076]
- 13 **Vachiéry JL**, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol* 2013; **62**: D100-D108 [PMID: 24355634 DOI: 10.1016/j.jacc.2013.10.033]
- 14 **Dupuis J**, Guazzi M. Pathophysiology and clinical relevance of pulmonary remodelling in pulmonary hypertension due to left heart diseases. *Can J Cardiol* 2015; **31**: 416-429 [PMID: 25840093 DOI: 10.1016/j.cjca.2014.10.012]
- 15 **Cheli M**, Vachiéry JL. Controversies in pulmonary hypertension due to left heart disease. *F1000Prime Rep* 2015; **7**: 07 [PMID: 25705390 DOI: 10.12703/P7-07]
- 16 **Bonderman D**, Ghio S, Felix SB, Ghofrani HA, Michelakis E, Mitrovic V, Oudiz RJ, Boateng F, Scalise AV, Roessig L, Semigran MJ. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation* 2013; **128**: 502-511 [PMID: 23775260 DOI: 10.1161/CIRCULATIONAHA.113.001458]
- 17 **Bonderman D**, Pretsch I, Steringer-Mascherbauer R, Jansa P, Rosenkranz S, Tufaro C, Bojic A, Lam CS, Frey R, Ochan Kilama M, Unger S, Roessig L, Lang IM. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. *Chest* 2014; **146**: 1274-1285 [PMID: 24991733 DOI: 10.1378/chest.14-0106]
- 18 **Lewis GD**, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. *Circulation* 2007; **115**: 59-66 [PMID: 17179022 DOI: 10.1161/CIRCULATIONAHA.106.626226]
- 19 **Matamis D**, Pampori S, Papathanasiou A, Papakonstantinou P, Tsigourias M, Galiatsou E, Koulouras V, Nakos G. Inhaled NO and sildenafil combination in cardiac surgery patients with out-of-proportion pulmonary hypertension: acute effects on postoperative gas exchange and hemodynamics. *Circ Heart Fail* 2012; **5**: 47-53 [PMID: 22057829 DOI: 10.1161/CIRCHEARTFAILURE.111.963314]
- 20 **de Miguel Díez J**, Chancafe Morgan J, Jiménez García R. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 305-312 [PMID: 23847414 DOI: 10.2147/COPD.S31236]
- 21 **Matamis D**, Tsigourias M, Papathanasiou A, Sineffaki H, Lepida D, Galiatsou E, Nakos G. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. *J Crit Care* 2014; **29**: 315.e7-315.14 [PMID: 24369757 DOI: 10.1016/j.jccr.2013.11.011]
- 22 **Wilkens H**, Lang I, Behr J, Berghaus T, Grohe C, Guth S, Hoeper MM, Kramm T, Krüger U, Langer F, Rosenkranz S, Schäfers HJ, Schmidt M, Seyfarth HJ, Wahlers T, Worth H, Mayer E. Chronic thromboembolic pulmonary hypertension (CTEPH): updated Recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011; **154** Suppl 1: S54-S60 [PMID: 22221974]

P- Reviewer: Inaba H, Kouraklis G, Rajagopala S, Riutta A

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Liu SQ



Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way

Raquel S Santos, Pedro L Silva, Paolo Pelosi, Patricia RM Rocco

Raquel S Santos, Pedro L Silva, Patricia RM Rocco, Laboratory of Pulmonary Investigation, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro 21941-902, Brazil

Paolo Pelosi, IRCCS AOU San Martino-IST, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, 16132 Genoa, Italy

Author contributions: Santos RS designed the review, conducted the literature review, wrote the article, and prepared the table; Silva PL designed the review, conducted the literature review, wrote the article, prepared the figure and table, and supervised all the process; Pelosi P and Rocco PRM wrote the article and supervised all the process.

Supported by Brazilian Council for Scientific and Technological Development (CNPq), Carlos Chagas Filho Rio de Janeiro State Research Foundation (FAPERJ), Department of Science and Technology (DECIT)/Brazilian Ministry of Health; and Coordination for the Improvement of Higher Level Personnel (CAPES).

Conflict-of-interest statement: Authors have no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Patricia RM Rocco, MD, PhD, Professor, Laboratory of Pulmonary Investigation, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Centro de Ciências da Saúde, Avenida Carlos Chagas Filho, s/n, Bloco G-014, Ilha do Fundão, Rio de Janeiro 21941-902, Brazil. prmrocco@gmail.com
Telephone: +55-21-39386530
Fax: +55-21-22808193

Received: May 30, 2015

Peer-review started: May 30, 2015

First decision: August 14, 2015

Revised: September 8, 2015

Accepted: October 20, 2015

Article in press: October 27, 2015

Published online: November 4, 2015

Abstract

Acute respiratory distress syndrome (ARDS) represents a serious problem in critically ill patients and is associated with in-hospital mortality rates of 33%-52%. Recruitment maneuvers (RMs) are a simple, low-cost, feasible intervention that can be performed at the bedside in patients with ARDS. RMs are characterized by the application of airway pressure to increase transpulmonary pressure transiently. Once non-aerated lung units are reopened, improvements are observed in respiratory system mechanics, alveolar re-aeration on computed tomography, and improvements in gas exchange (functional recruitment). However, the reopening process could lead to vascular compression, which can be associated with overinflation, and gas exchange may not improve as expected (anatomical recruitment). The purpose of this review was to discuss the effects of different RM strategies - sustained inflation, intermittent sighs, and stepwise increases of positive end-expiratory pressure (PEEP) and/or airway inspiratory pressure - on the following parameters: hemodynamics, oxygenation, barotrauma episodes, and lung recruitability through physiological variables and imaging techniques. RMs and PEEP titration are interdependent events for the success of ventilatory management. PEEP should be adjusted on the basis of respiratory system mechanics and oxygenation. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (*i.e.*, that providing the best balance of benefit and harm) and

the effects of RMs on clinical outcome are still under discussion, and further evidence is needed.

Key words: Recruitment maneuvers; Acute respiratory distress syndrome; Positive end-expiratory pressure; Transpulmonary pressure; Lung ultrasonography

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Experimental and clinical studies show that stepwise recruitment maneuvers (RMs) improve oxygenation and lung aeration and are associated with less hemodynamic instability and inflammatory impact on lung tissue compared to traditional abrupt maneuvers. Patients with severe acute respiratory distress syndrome, characterized by increased edema and atelectasis, are good candidates for RMs. Patients whose oxygenation improves with increased pressure are at lower risk of death. Post-recruitment positive end-expiratory pressure (PEEP) titration is critical to maintaining stabilization of alveolar units and avoiding derecruitment. The use of individualized PEEP based on lung compliance might move clinical management forward.

Santos RS, Silva PL, Pelosi P, Rocco PRM. Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way. *World J Crit Care Med* 2015; 4(4): 278-286 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i4/278.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i4.278>

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is clinically characterized by severe hypoxemia, reduced lung compliance, and bilateral radiographic infiltrates^[1]. Protective mechanical ventilation strategies, which are characterized by protective tidal volumes [$V_T = 6$ mL/kg, predicted body weight (PBW)] and end-inspiratory (plateau) airway pressures lower than 28 cm H₂O, have been associated with improved survival in randomized clinical trials^[2,3]. However, the use of protective V_T alone seems to be not enough to maintain homogeneous distribution of ventilation across different alveolar units^[4]. In this line, V_T titrated to 6 mL/kg (PBW) may result in repetitive opening and closing of such units, which may result in atelectrauma unless sufficient positive end-expiratory pressure (PEEP) is applied. On the other hand, overdistension and disruption of alveolar units may develop if high PEEP values are used^[5].

General anesthesia and neuromuscular blockade may potentiate the generation of atelectatic areas^[6]. In a normal homeostatic condition, the sigh reflex maintains lung compliance and decreases atelectasis^[7]. However, during mechanical ventilation, there is no sigh reflex. One possibly way to maintain oxygenation, functional residual capacity, and respiratory system elastance is the application of recruitment maneuvers (RMs), which

have become a component of lung-protective ventilation strategies^[8,9]. A recent systematic review suggested that, when included in ventilatory strategies, RMs reduced mortality by 6% in patients with moderate to severe ARDS^[10]. Since this is only a slight improvement in mortality and no major differences in length of intensive care unit or hospital stay were observed, subsequent studies raised concerns regarding the beneficial effects and the safety of RMs.

This review sought to discuss: (1) the physiologic effects of RMs; (2) describe different types of RMs and their safety; (3) techniques of positive end-expiratory pressure titration; and (4) the future perspectives of RMs in the presence of protective ventilation strategies.

PHYSIOLOGICAL EFFECTS OF RMS

A RM is a dynamic, transient increase in transpulmonary pressure (difference between airway pressure and pleural pressure) which is directly proportional to the reopening of lung units. Its success and/or adverse events can be predicted by the magnitude of transpulmonary pressure, balancing the increase in aerated lung areas and the reduction of mechanical stress between the edge of collapsed and aerated areas^[11]. Traditionally, RMs usually improve lung mechanics and oxygenation, but whether these are the only positives consequences of RM use remains unknown. Thus far, no randomized clinical trial has aimed to show whether the presence or absence of RM among the constituent elements of a protective ventilator strategy bundle makes a difference. A randomized clinical trial designed to answer this question with sufficient statistical power, the alveolar recruitment for ARDS trial, is ongoing. Nevertheless, important, physiologically based studies have attempted to answer key questions. In a prospective study of 16 mechanically ventilated patients with ARDS by Di Marco *et al.*^[12] divided participants into responders and non-responders based on an increase in diffusing capacity for carbon monoxide associated with a higher PEEP. Increasing PEEP from 5 to 15 cm H₂O has been demonstrated to yield increased lung volume (anatomical recruitment) in half of patients, while in other patients, higher PEEP results in improvement of lung volume and perfusion (functional recruitment). In other words, opening of alveolar units does not necessarily entail restoration of lung perfusion in that specific region. In cases of functional recruitment, an increment in PaO₂/FiO₂ can be expected (Figure 1).

The viscoelastance and time-dependent force required to open collapsed areas is a function of both transpulmonary pressure and time^[13], known as the pressure-time product. In an attempt to evaluate optimal RM duration and hemodynamic changes, Amal *et al.*^[14] conducted a prospective clinical trial of 12 recruited patients with ARDS. The authors found that most recruitment occurs in the first few seconds of a sustained inflation, suggesting that time is less important as a determinant of RM success. Instead, time plays a critical

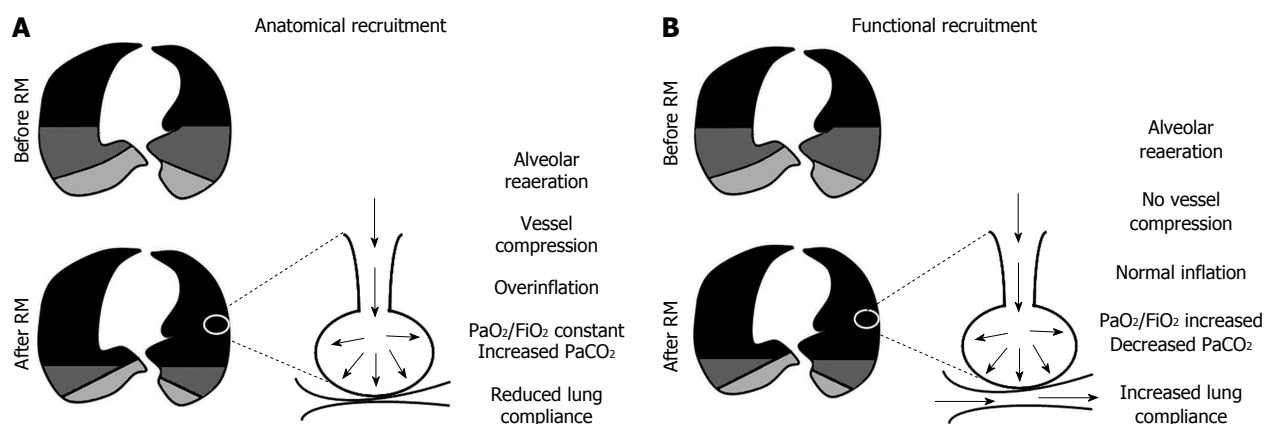


Figure 1 Schematic representation of lung morphology before and after application of recruitment maneuvers. A: Anatomical recruitment. Alveolar reopening is not accompanied by reperfusion and PaO₂/FiO₂ remains unchanged; B: Functional recruitment. Reperfusion is a landmark of functional recruitment and, after application of a recruitment maneuver, an increment in PaO₂/FiO₂ ratio is expected. RM: Recruitment maneuver.

role in hemodynamic alterations, which generally occur with a longer duration of inflation.

RMs are largely related to reversal of atelectasis in the context of ARDS. Moreover, their beneficial effects have also been described in patients under general anesthesia, during postoperative ventilation, and in other conditions related to hypoxemia, including heart failure^[7,15].

TYPES OF RMS

Tables 1 and 2 summarize clinical and experimental studies comparing different RM methods according to Population, Intervention, Comparison, Outcome criteria. Sigh was the first reported RM, applied interposed with monotonous ventilation to mimic physiological breathing as it occurs in healthy subjects^[16]. This RM consists of high V_T in controlled mode or high PEEP up to a specific plateau pressure level, for a selected number of cycles. In this line, Pelosi *et al.*^[17], in an observational study, ventilated 10 ARDS patients for 1 h with a lung-protective strategy consisting of three consecutive sighs/minute at 45 cm H₂O plateau pressure. These patients exhibited improvement in oxygenation, lung elastance, and functional residual capacity compared to patients who did not receive sighs. Despite the beneficial effects of this maneuver, high sigh frequency (up to 180/h) was associated with hyperinflation and expression of type III procollagen mRNA in lung tissue in experimental models^[18]. Lower sigh frequency can protect the lung^[18], mainly when combined with pressure-support ventilation^[19].

The most widely described RM is sustained inflation, in which airway pressure is abruptly raised for a given time interval. A common sustained inflation is 40 cm H₂O for 40 s^[20-22]. More recently, RMs with a stepwise increase in airway pressure and/or PEEP (stepwise RM) have been proposed to provide slowly increasing transpulmonary pressure instead of the rapid increase used in sustained inflation, in experimental^[8,23,24] and clinical studies^[25-27]. Both sustained inflation (fast RM) and stepwise RM (slow

RM) have been reported to improve oxygenation and lung function and minimize atelectasis in experimental^[8,24,28] and clinical scenarios^[20,25]. Since stepwise RMs recruit lung units as effectively as sustained inflation with a lower mean airway pressure, they may lead to less hemodynamic compromise and hyperinflation. In this context, sustained inflation has also been associated with risk of hypotension^[29], barotrauma^[29], and has even been reported to be ineffective in improving oxygenation and reducing intrapulmonary shunting^[30]. In an observational study and randomized controlled trial, respectively, stepwise RM improved lung compliance, shunt fraction, and oxygen saturation^[25] and was associated with less release of inflammatory mediators^[24] compared to a ventilator strategy that did not incorporate RMs. However, stepwise RMs may have a heterogeneous impact on respiratory mechanics and cause adverse hemodynamic effects in an observational clinical study^[26]. In experimental endotoxin-induced mild ARDS, stepwise RM, compared to sustained inflation, was associated with reduced type II epithelial cell damage and decreased expression of markers associated with fibrosis and endothelial cell damage, depending on ARDS etiology^[8].

Despite extensive research into the applications of RMs, definitive guidelines for these maneuvers have not been established. As a step toward standardization, a trial with high methodological quality is being conducted to assess the 28-d survival of ARDS patients subjected to maximum stepwise alveolar recruitment followed by ventilation with PEEP titrated according to best compliance^[31]. This multicenter study may represent a valuable contribution to the treatment of patients with ARDS^[31].

Assisted ventilation may be associated with homogeneous lung recruitment. In the presence of lung recruitment, end-expiratory lung volume increases, thus reducing strain, while lung elastance decreases, resulting in lower inspiratory transpulmonary pressure and stress^[32]. However, in the absence of lung recruitment, transpulmonary pressure might be higher than during controlled mechanical ventilation and thus,

Table 1 Recruitment maneuver methods and outcomes reported in the literature about clinical studies

Ref.	Population	Design	Interventions	Comparison	Outcome
Pelosi <i>et al</i> ^[27]	Patients with pulmonary and extrapulmonary ARDS	Observational study	3 sighs/min at Pplat 45 cm H ₂ O, V _T to maintain Pplat ≤ 35 cm H ₂ O. PEEP level to keep the lung open	(1) 1 h of ventilator strategy; (2) 2 h of ventilator strategy; and (3) 1 h of ventilator strategy with three consecutive sighs/min at Pplat 45 cm H ₂ O	Sigh during protective ventilation improved lung recruitment
Borges <i>et al</i> ^[44]	Patients with early ARDS	Observational study	Stepwise maximum-recruitment strategy with sequential increments in Paw, in 5-cm H ₂ O steps, until the detection of PaO ₂ + PaCO ₂ = 400 mmHg	No comparisons	Stepwise maximum recruitment reverted hypoxemia and fully recruited the lungs
Meade <i>et al</i> ^[29]	Patients with ARDS (PaO ₂ /FiO ₂ ≤ 250 mmHg)	Randomized controlled trial	Low V _T , Pplat ≤ 30 cm H ₂ O or ≥ 40 cm H ₂ O, and lower or higher PEEP levels according to PEEP/FiO ₂ table	(1) Ventilator strategy with Pplat ≤ 30 cm H ₂ O, and conventional PEEP levels; (2) “open lung” approach with Pplat ≤ 40 cm H ₂ O, RM, and higher PEEP levels	“Open-lung” approach improved oxygenation associated with lower use of rescue therapies
Hodgson <i>et al</i> ^[25]	Patients with early ARDS	Observational study	Staircase RM, Paw set to 15 cm H ₂ O above the PEEP, which was increased in a stepwise manner to 20, 30 and then 40 cm H ₂ O every 2 min, followed by PEEP titration	No comparisons	80% of early ARDS patients responded to staircase RM
Hodgson <i>et al</i> ^[27]	Patients with ARDS	Randomized controlled trial	Control ventilation strategy compared to staircase recruitment maneuver	(1) Control group: PCV, Pplat < 30 cm H ₂ O, V _T < 6 mL/kg. FiO ₂ adjusted to SaO ₂ : 90% to 92%; and (2) Staircase RM: Paw adjusted to 15 cm H ₂ O above PEEP level, which was increased in a stepwise manner to 20, 30 and 40 cm H ₂ O every 2 min, and then reduced in steps of 2.5 from 25 to 15 cm H ₂ O every 3 min until a decrease in SaO ₂ ≥ 1%	Staircase RM improved plasma cytokines, oxygenation and lung function over 7 d
Morán <i>et al</i> ^[26]	Patients with early ARDS	Observational study	Stepwise RM started from plateau pressure/PEEP of 40/25 cm H ₂ O, 5 cm H ₂ O of PEEP was sequentially increased until PaO ₂ /FiO ₂ of 350 mmHg or plateau pressure/PEEP of 60/40 cm H ₂ O	No comparisons	Stepwise RM improved oxygenation but caused hemodynamic instability and transient hypoxemia

Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. ARDS: Acute respiratory distress syndrome; FiO₂: Inspiratory oxygen fraction; PaO₂: Arterial oxygen partial pressure; PaCO₂: Arterial carbon dioxide partial pressure; PCV: Pressure-controlled ventilation; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; SaO₂: Arterial oxygen saturation; V_T: Tidal volume.

assisted ventilation may lead to deleterious effects^[33,34]. Additionally, spontaneous breathing during assisted mechanical ventilation may exacerbate lung injury by increasing patient-ventilator asynchrony and rapid shallow breathing^[35]. Furthermore, negative pleural pressures may increase intrathoracic blood volume, worsening pulmonary edema and lung damage^[36]. In short, we suggest that assisted mechanical ventilation can be applied for mild and moderate ARDS.

It is well established that prone positioning improves oxygenation in patients who require mechanical ventilatory support for management of ARDS^[37]. Guérin *et al*^[38] recently showed that early application of prolonged prone positioning significantly reduces mortality in patients with severe ARDS. Pronation acts as a RM, increasing transpulmonary pressure in dorsal regions and reducing alveolar instability and hyperinflation. In this line, Galiatsou *et al*^[39] assessed lung computed tomography findings in ARDS patients in the supine and prone positions after RM application. The authors found that prone position had an additive effect on oxygenation and recruitment of dependent lung regions, and was

associated with a reduction in ventral overinflation areas. These findings were confirmed by Cornejo *et al*^[40] who evaluated the interaction of lung recruitability, high PEEP values, and prone positioning. Reductions in atelectasis and/or overdistension were observed in patients in both categories (low and high recruitability) at both low and high PEEP in the prone position. Furthermore, in a subgroup of patients with high recruitability, prone positioning added to the effect of high PEEP on atelectrauma, and prevented its effects on tidal overinflation.

SAFETY OF RMS

RMs are being increasingly used in clinical practice, and even if full re-expansion is expected, negative effects can occur, especially on hemodynamics. The type of RM seems to be a crucial predictor of hemodynamic adverse effects. In a prospective clinical trial, Iannuzzi *et al*^[41] evaluated hemodynamic changes in 40 patients with ARDS randomized to receive RMs with sustained inflation or pressure-controlled ventilation (PCV) adjusted to generate the same pressure-time product. PCV-RM,

Table 2 Recruitment maneuver methods and outcomes reported in the literature about experimental studies

Ref.	Population	Design	Interventions	Comparison	Outcome
Rzezinski <i>et al</i> ^[23]	Animals with mild extrapulmonary lung injury	Randomized experimental study	Prolonged RM stepwise increase in PIP of 15-20-25 cm H ₂ O above a PEEP of 15 cm H ₂ O (maximal PIP = 40 cm H ₂ O)	(1) Animals ventilated with V _T = 6 mL/kg and PEEP = 5 cm H ₂ O with no RMs; (2) Sustained inflation (40 cm H ₂ O for 40 s); or (3) Stepwise increase in Paw of 15, 20, 25 cm H ₂ O above a PEEP of 15 cm H ₂ O (maximal PIP = 40 cm H ₂ O), with interposed periods of Paw = 10 cm H ₂ O above a PEEP = 15 cm H ₂ O	Prolonged RM improved lung function, with less damage to alveolar epithelium, resulting in reduced pulmonary injury
Steimback <i>et al</i> ^[18]	Animals with extrapulmonary lung injury	Randomized experimental study	Sigh with different PIP and frequencies	(1) Animals ventilated with V _T = 6 mL/kg and PEEP = 5 cm H ₂ O with no RMs; (2) Sustained inflation (40 cm H ₂ O for 40 s); (3) RM (180 sighs/h) and PIP (40 cm H ₂ O) (S180/40); (4) RM (10 sighs/h) and PIP (40 cm H ₂ O) (S10/40); and (5) RM (10 sighs/h) and PIP (20 cm H ₂ O) (S10/20)	The reduction in sigh frequency led to a protective effect on the lung and distal organs
Silva <i>et al</i> ^[8]	Animals with pulmonary and extrapulmonary lung injury	Randomized experimental study	Stepwise RM (5 cm H ₂ O/step, 8.5 s at each step during 51 s); Stepwise RM (5 cm H ₂ O/step, 5 s at each step during 30 s)	(1) Sustained inflation (30 cm H ₂ O for 30 s); (2) Stepwise PIP increase 30 cm H ₂ O over 51 s (STEP-51); and (3) Stepwise PIP increase over 30 s with maximum PIP sustained for a further 30 s (STEP-30/30)	Stepwise RM prevented fibrogenesis and endothelial cell damage

Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; V_T: Tidal volume.

compared to sustained inflation, resulted in greater oxygenation and less hemodynamic impairment as reflected by lower central venous and pulmonary artery pressures, lower right ventricle workload, and higher cardiac output. In addition, the post-RM level of PEEP and lung recruitability should be taken into account to avoid complications related to high intrathoracic pressure during RMs^[42,43].

Desaturation and barotrauma are less common complications of RMs. Hodgson *et al*^[25], demonstrated that although 8 of 20 patients desaturated and exhibited transient circulatory depression during application of RMs, they had improved shunt fraction, oxygenation, and respiratory system compliance 60 min after maneuver application followed by PEEP titration. In a randomized controlled trial by Meade *et al*^[29], five patients with ARDS developed ventilator asynchrony, three experienced discomfort during the RM, two had hypotension, and four developed barotrauma. However, some issues should be taken into account, such as the sedation protocol allowing spontaneous cycles during the application of a sustained maneuver for 40 s. In addition, the level of PEEP was returned to the same value as before RM application. On the other hand, in a previous observational study, Borges *et al*^[44] demonstrated that two of 26 patients developed barotrauma; one case occurred 24 h and the other 12 h after application of the RM. Despite the preceding reports, recent data confirm that RMs are not associated with an increased risk of barotrauma^[10,45].

Lung recruitability could provide valuable information before RM application to prevent possible deleterious effects. Oxygenation and respiratory system elastance are often used to evaluate response to RMs. Gattinoni *et al*^[42] aimed to establish an estimation of lung recruitability in patients with ARDS based on three physiological variables: Oxygenation, respiratory

system compliance, and alveolar dead space in patients exposed to a progressive increase in PEEP. However, these variables had low sensitivity and specificity to predict higher lung recruitability. Static lung compliance (the difference between respiratory system compliance and chest wall compliance) reflects transpulmonary pressure as well as lung recruitment, and could be used instead of respiratory system compliance to measure lung recruitability^[46]. Esophageal pressure monitoring permits measurement of lung compliance, but its implementation in the intensive care unit setting is still a challenge. In research settings, computed tomography can be used to assess recruitment, as well as to individualize ventilation strategies in order to keep the lungs open^[45,47,48]. Additionally, the use of lung ultrasonography (LUS) can be a useful imaging tool to assess lung aeration in critically ill patients^[49,50]. In this context, studies have shown the utility of LUS in the detection and quantification of lung recruitment *via* a transesophageal approach^[51] and *via* a transthoracic approach^[50]. Electrical impedance tomography (EIT) can provide a good estimate of the amount of tidal recruitment and may be useful to individualize ventilatory settings^[52,53]. Even though LUS and EIT offer, at the bedside, an easy, alternative way to evaluate lung recruitment, both are inappropriate to detect hyperinflation.

Response to RMs and/or lung recruitability cannot be predicted *a priori*, and require individualized assessment. Recently, Cressoni *et al*^[47] showed that extent of lung inhomogeneities increases as poorly aerated tissue increases from mild to severe ARDS (from 14% to 23%). In this study, high lung recruitability was considered in patients in whom the poorly aerated tissue area decreased with increasing PEEP, unlike in patients in whom poorly aerated tissue increased with increasing

pressure^[47]. Additionally, poorly aerated tissue areas, *i.e.*, areas of tidal recruitment/derecruitment, are the primary targets of the inflammatory process in ventilator-induced lung injury^[54]. In this context, severe ARDS is more recruitable than mild or moderate disease^[42,47], and extrapulmonary ARDS is more recruitable than cases of pulmonary etiology. Several studies^[55-57] have demonstrated that focal lung injury (pulmonary etiology) is associated with lower recruitability and alveolar overinflation in response to increased PEEP levels. In contrast, within the group of ARDS responders, in those with diffuse loss of aeration (extrapulmonary etiology), alveolar recruitment resulting from PEEP is not accompanied by lung overinflation^[42,55].

Recently, Caironi *et al.*^[58] retrospectively analyzed a large cohort of patients with ARDS, aiming to describe lung edema and recruitability according to the Berlin definition and elucidate whether assessment of PaO₂/FiO₂ at standardized PEEP (5 or 15 cm H₂O) allows a more accurate description of ARDS severity as compared to its clinical assessment. They reported that the clinical PEEP applied when assessing PaO₂/FiO₂ may mask the underlying ARDS severity, and that application of the Berlin definition at 5 cm H₂O PEEP more accurately matches ARDS lung injury severity and recruitability, providing important information to guide ventilator strategies and to assess mortality risk.

TITRATION OF POSITIVE END-EXPIRATION PRESSURE

PEEP is required to recruit or maintain recruitment in the heterogeneous ARDS lung. The most common method for PEEP level selection is the use of PEEP/FiO₂ tables, introduced by the ARDS Network^[3] and the LOVS study^[29]. Although high PEEP values improve oxygenation and decrease alveolar stress^[44], they can sometimes result in lung overdistension and hemodynamic instability^[59]. An explanation for this discrepancy may be found in the heterogeneity of ARDS: A subpopulation of non-responders (patients with low recruitability) experience no change in arterial oxygenation with higher PEEP^[60], and may be at greater risk of ventilator-induced lung injury from overdistension^[61]. On the other hand, patients with predominantly recruitable lung (severe ARDS; PaO₂/FiO₂ < 150 mmHg) exhibit an association of oxygenation response and PEEP adjustment, as well as lower risk of death^[62]. Recently, a Cochrane review of seven trials concluded that high PEEP levels are unrelated to hospital outcome as compared with low levels^[63]. A relationship between higher PEEP and low mortality could be achieved in patients with more severe ARDS, in whom lung recruitability is higher^[59]. In the era of identification of PEEP responders and/or high recruitability, attention to prevention of intratidal collapse and decollapse ("open the lung and keep it open!")^[64] and lung function seems to be more relevant than oxygenation.

In a study of 57 patients with ARDS, Huh *et al.*^[65]

compared daily decremental PEEP titration according to the best dynamic compliance performed after an RM vs PEEP selection as suggested by ARDSnet^[3], based on a PEEP/FiO₂ table. In this protocol, an initial improvement in oxygenation occurred in patients who received decremental PEEP titration after RM compared to those in whom the PEEP/FiO₂ table method was used. This earlier improvement in oxygenation was not related to any advantage in respiratory mechanics within 1 wk, nor with 28-d intensive care unit mortality.

Cressoni *et al.*^[66] reported that, in mechanically ventilated patients in the supine position, collapse occurs first in the most dependent areas and overinflation in the less dependent regions, as observed on computed tomography analysis. This finding calls into question the use of a single pressure parameter to reflect the entire lung structure. Pintado *et al.*^[67], in a randomized controlled pilot study, suggested that PEEP application according to the highest compliance was associated with more organ dysfunction-free days and a trend toward lower mortality at 28 d as compared with FiO₂-guided PEEP selection, with no differences in oxygenation ratio or PEEP level among groups.

The new concept of transpulmonary pressure to titrate PEEP during the decremental method has emerged as a measurement of alveolar stability and alveolar stress. Rodriguez *et al.*^[68] showed that high and low transpulmonary pressure values were associated with lung overdistension and with reductions in oxygenation and collapse, respectively. In addition, a positive correlation has been observed between transpulmonary and airway pressures. Transpulmonary pressure reflects pleural pressure surrounding dependent lung regions at a given point, while airway pressure only reflects opened alveolar units. In this context, transpulmonary pressure could be a more representative measure to guide PEEP selection and prevent alveolar unit instability.

"Open-lung PEEP", first described more than 2 decades ago by Lachmann *et al.*^[64], represents the level of PEEP that combines the minimal tidal recruitment/derecruitment, overinflation, and dead space with optimal oxygenation and lung compliance. Open-lung PEEP should be achieved after an application of RM^[44], which may open collapsed alveolar units, and should then be titrated gradually toward the minimum value that can stabilize the previously recruited lung^[67]. RMs and PEEP titration are interdependent events for the success of ventilatory management.

CONCLUSION

RMs are a simple, low-cost, feasible intervention that can be performed at bedside in intensive care units. A wealth of experimental and clinical data has demonstrated improvements in oxygenation, lung mechanics, and lung re-aeration after application of RMs. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (*i.e.*, that with the

best balance of benefit and harm) and the effects of RMs on clinical outcome are still under discussion, and further evidence is needed.

ACKNOWLEDGMENTS

We express our gratitude to Mrs. Moira Elizabeth Schottler and Mr. Filipe Vasconcellos for their assistance in editing the manuscript.

REFERENCES

- Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**: 2526-2533 [PMID: 22797452 DOI: 10.1001/jama.2012.5669]
- Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; **303**: 865-873 [PMID: 20197533 DOI: 10.1001/jama.2010.218]
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]
- Treschan TA, Beiderlinden M. Role of recruitment maneuvers for lung-protective ventilation in the operating room remains unclear. *Anesthesiology* 2015; **122**: 472-473 [PMID: 25603214 DOI: 10.1097/ALN.0000000000000549]
- Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013; **369**: 2126-2136 [PMID: 24283226 DOI: 10.1056/NEJMr1208707]
- Spieth PM, Guldner A, Uhlig C, Bluth T, Kiss T, Schultz MJ, Pelosi P, Koch T, Gama de Abreu M. Variable versus conventional lung protective mechanical ventilation during open abdominal surgery: study protocol for a randomized controlled trial. *Trials* 2014; **15**: 155 [PMID: 24885921 DOI: 10.1186/1745-6215-15-155]
- Hartland BL, Newell TJ, Damico N. Alveolar recruitment maneuvers under general anesthesia: a systematic review of the literature. *Respir Care* 2015; **60**: 609-620 [PMID: 25425708 DOI: 10.4187/respcare.03488]
- Silva PL, Moraes L, Santos RS, Samary C, Ramos MB, Santos CL, Morales MM, Capelozzi VL, Garcia CS, de Abreu MG, Pelosi P, Marini JJ, Rocco PR. Recruitment maneuvers modulate epithelial and endothelial cell response according to acute lung injury etiology. *Crit Care Med* 2013; **41**: e256-e265 [PMID: 23887231 DOI: 10.1097/CCM.0b013e31828a3c13]
- Keenan JC, Formenti P, Marini JJ. Lung recruitment in acute respiratory distress syndrome: what is the best strategy? *Curr Opin Crit Care* 2014; **20**: 63-68 [PMID: 24335655 DOI: 10.1097/MCC.0000000000000054]
- Suzumura EA, Figueiró M, Normilio-Silva K, Laranjeira L, Oliveira C, Buehler AM, Bugano D, Passos Amato MB, Ribeiro Carvalho CR, Berwanger O, Cavalcanti AB. Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Intensive Care Med* 2014; **40**: 1227-1240 [PMID: 25097070 DOI: 10.1007/s00134-014-3413-6]
- Brunner JX, Wysocki M. Is there an optimal breath pattern to minimize stress and strain during mechanical ventilation? *Intensive Care Med* 2009; **35**: 1479-1483 [PMID: 19543882 DOI: 10.1007/s00134-009-1510-8]
- Di Marco F, Devaquet J, Lyazidi A, Galia F, da Costa NP, Fumagalli R, Brochard L. Positive end-expiratory pressure-induced functional recruitment in patients with acute respiratory distress syndrome. *Crit Care Med* 2010; **38**: 127-132 [PMID: 19730254 DOI: 10.1097/CCM.0b013e3181b4a7e7]
- Marini JJ, Gattinoni L. Propagation prevention: a complementary mechanism for "lung protective" ventilation in acute respiratory distress syndrome. *Crit Care Med* 2008; **36**: 3252-3258 [PMID: 18936705 DOI: 10.1097/CCM.0b013e31818f0e68]
- Arnall JM, Paquet J, Wysocki M, Demory D, Donati S, Granier I, Corno G, Durand-Gasselin J. Optimal duration of a sustained inflation recruitment maneuver in ARDS patients. *Intensive Care Med* 2011; **37**: 1588-1594 [PMID: 21858522 DOI: 10.1007/s00134-011-2323-0]
- Constantin JM, Futier E, Cherprenet AL, Chanques G, Guerin R, Cayot-Constantin S, Jabaudon M, Perbet S, Chartier C, Jung B, Guelon D, Jaber S, Bazin JE. A recruitment maneuver increases oxygenation after intubation of hypoxemic intensive care unit patients: a randomized controlled study. *Crit Care* 2010; **14**: R76 [PMID: 20426859 DOI: 10.1186/cc8989]
- Levine M, Gilbert R, Auchincloss JH. A comparison of the effects of sighs, large tidal volumes, and positive end expiratory pressure in assisted ventilation. *Scand J Respir Dis* 1972; **53**: 101-108 [PMID: 5052722]
- Pelosi P, Cadringer P, Bottino N, Panigada M, Carrieri F, Riva E, Lissoni A, Gattinoni L. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **159**: 872-880 [PMID: 10051265 DOI: 10.1164/ajrcm.159.3.9802090]
- Steinback PW, Oliveira GP, Rzezinski AF, Silva PL, Garcia CS, Rangel G, Morales MM, Lapa E Silva JR, Capelozzi VL, Pelosi P, Rocco PR. Effects of frequency and inspiratory plateau pressure during recruitment manoeuvres on lung and distal organs in acute lung injury. *Intensive Care Med* 2009; **35**: 1120-1128 [PMID: 19221714 DOI: 10.1007/s00134-009-1439-y]
- Moraes L, Santos CL, Santos RS, Cruz FF, Saddy F, Morales MM, Capelozzi VL, Silva PL, de Abreu MG, Garcia CS, Pelosi P, Rocco PR. Effects of sigh during pressure control and pressure support ventilation in pulmonary and extrapulmonary mild acute lung injury. *Crit Care* 2014; **18**: 474 [PMID: 25113136 DOI: 10.1186/s13054-014-0474-4]
- Oczenski W, Hörmann C, Keller C, Lorenz N, Kepka A, Schwarz S, Fitzgerald RD. Recruitment maneuvers after a positive end-expiratory pressure trial do not induce sustained effects in early adult respiratory distress syndrome. *Anesthesiology* 2004; **101**: 620-625 [PMID: 15329586]
- Oczenski W, Hörmann C, Keller C, Lorenz N, Kepka A, Schwarz S, Fitzgerald RD. Recruitment maneuvers during prone positioning in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; **33**: 54-61; quiz 62 [PMID: 15644648]
- Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 2004; **32**: 1018-1027 [PMID: 15071395]
- Rzezinski AF, Oliveira GP, Santiago VR, Santos RS, Ornellas DS, Morales MM, Capelozzi VL, Amato MB, Conde MB, Pelosi P, Rocco PR. Prolonged recruitment manoeuvre improves lung function with less ultrastructural damage in experimental mild acute lung injury. *Respir Physiol Neurobiol* 2009; **169**: 271-281 [PMID: 19819351 DOI: 10.1016/j.resp.2009.10.002]
- Silva PL, Moraes L, Santos RS, Samary C, Ornellas DS, Maron-Gutierrez T, Morales MM, Saddy F, Capelozzi VL, Pelosi P, Marini JJ, Gama de Abreu M, Rocco PR. Impact of pressure profile and duration of recruitment maneuvers on morphofunctional and biochemical variables in experimental lung injury. *Crit Care Med* 2011; **39**: 1074-1081 [PMID: 21263326 DOI: 10.1097/CCM.0b013e318206d69a]
- Hodgson CL, Tuxen DV, Bailey MJ, Holland AE, Keating JL, Pilcher D, Thomson KR, Varma D. A positive response to a recruitment maneuver with PEEP titration in patients with ARDS, regardless of transient oxygen desaturation during the maneuver. *J Intensive Care Med* 2011; **26**: 41-49 [PMID: 21262752 DOI: 10.1177/0885066610383953]
- Morán I, Blanch L, Fernández R, Fernández-Mondéjar E, Zavala

- E, Mancebo J. Acute physiologic effects of a stepwise recruitment maneuver in acute respiratory distress syndrome. *Minerva Anestesiol* 2011; **77**: 1167-1175 [PMID: 21623343]
- 27 **Hodgson CL**, Tuxen DV, Davies AR, Bailey MJ, Higgins AM, Holland AE, Keating JL, Pilcher DV, Westbrook AJ, Cooper DJ, Nichol AD. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Crit Care* 2011; **15**: R133 [PMID: 21635753 DOI: 10.1186/cc10249cc10249]
 - 28 **Riva DR**, Oliveira MB, Rzezinski AF, Rangel G, Capelozzi VL, Zin WA, Morales MM, Pelosi P, Rocco PR. Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury. *Crit Care Med* 2008; **36**: 1900-1908 [PMID: 18496360 DOI: 10.1097/CCM.0b013e3181760e5d]
 - 29 **Meade MO**, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299**: 637-645 [PMID: 18270352 DOI: 10.1001/jama.299.6.637299/6/637]
 - 30 **Villagrà A**, Ochagavía A, Vatua S, Murias G, Del Mar Fernández M, Lopez Aguilar J, Fernández R, Blanch L. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; **165**: 165-170 [PMID: 11790648 DOI: 10.1164/ajrcm.165.2.2104092]
 - 31 **ART Investigators**. Rationale, study design, and analysis plan of the Alveolar Recruitment for ARDS Trial (ART): study protocol for a randomized controlled trial. *Trials* 2012; **13**: 153 [PMID: 22929542 DOI: 10.1186/1745-6215-13-153]
 - 32 **Saddy F**, Sutherasan Y, Rocco PR, Pelosi P. Ventilator-associated lung injury during assisted mechanical ventilation. *Semin Respir Crit Care Med* 2014; **35**: 409-417 [PMID: 25105820 DOI: 10.1055/s-0034-1382153]
 - 33 **Yoshida T**, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, Tucci MR, Zin WA, Kavanagh BP, Amato MB. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013; **188**: 1420-1427 [PMID: 24199628 DOI: 10.1164/rccm.201303-0539OC]
 - 34 **Güldner A**, Kiss T, Bluth T, Uhlig C, Braune A, Carvalho N, Quast T, Rentzsch I, Huhle R, Spieth P, Richter T, Saddy F, Rocco PR, Kasper M, Koch T, Pelosi P, de Abreu MG. Effects of ultraproductive ventilation, extracorporeal carbon dioxide removal, and spontaneous breathing on lung morphofunction and inflammation in experimental severe acute respiratory distress syndrome. *Anesthesiology* 2015; **122**: 631-646 [PMID: 25371037 DOI: 10.1097/ALN.0000000000000504]
 - 35 **Thille AW**, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; **32**: 1515-1522 [PMID: 16896854 DOI: 10.1007/s00134-006-0301-8]
 - 36 **Kallet RH**, Alonso JA, Luce JM, Matthay MA. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. *Chest* 1999; **116**: 1826-1832 [PMID: 10593817]
 - 37 **Guérin C**. Prone ventilation in acute respiratory distress syndrome. *Eur Respir Rev* 2014; **23**: 249-257 [PMID: 24881080 DOI: 10.1183/09059180.00001114]
 - 38 **Guérin C**, Reignier J, Richard JC. Prone positioning in the acute respiratory distress syndrome. *N Engl J Med* 2013; **369**: 980-981 [PMID: 24004127 DOI: 10.1056/NEJMc1308895]
 - 39 **Galiatsou E**, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006; **174**: 187-197 [PMID: 16645177 DOI: 10.1164/rccm.200506-899OC]
 - 40 **Cornejo RA**, Díaz JC, Tobar EA, Bruhn AR, Ramos CA, González RA, Repetto CA, Romero CM, Gálvez LR, Llanos O, Arellano DH, Neira WR, Diaz GA, Zamorano AJ, Pereira GL. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013; **188**: 440-448 [PMID: 23348974 DOI: 10.1164/rccm.201207-1279OC]
 - 41 **Iannuzzi M**, De Sio A, De Robertis E, Piazza O, Servillo G, Tufano R. Different patterns of lung recruitment maneuvers in primary acute respiratory distress syndrome: effects on oxygenation and central hemodynamics. *Minerva Anestesiol* 2010; **76**: 692-698 [PMID: 20820146]
 - 42 **Gattinoni L**, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; **354**: 1775-1786 [PMID: 16641394 DOI: 10.1056/NEJMoa052052]
 - 43 **Lim CM**, Jung H, Koh Y, Lee JS, Shim TS, Lee SD, Kim WS, Kim DS, Kim WD. Effect of alveolar recruitment maneuver in early acute respiratory distress syndrome according to antiderecruitment strategy, etiological category of diffuse lung injury, and body position of the patient. *Crit Care Med* 2003; **31**: 411-418 [PMID: 12576945 DOI: 10.1097/01.CCM.0000048631.88155.39]
 - 44 **Borges JB**, Okamoto VN, Matos GF, Caramaz MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; **174**: 268-278 [PMID: 16690982 DOI: 10.1164/rccm.200506-976OC]
 - 45 **de Matos GF**, Stanzani F, Passos RH, Fontana MF, Albaladejo R, Caserta RE, Santos DC, Borges JB, Amato MB, Barbas CS. How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography. *Crit Care* 2012; **16**: R4 [PMID: 22226331 DOI: 10.1186/cc10602]
 - 46 **Akoumianaki E**, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, Guérin C, Patroniti N, Ranieri VM, Gattinoni L, Nava S, Terragni PP, Pesenti A, Tobin M, Mancebo J, Brochard L. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014; **189**: 520-531 [PMID: 24467647 DOI: 10.1164/rccm.201312-2193CI]
 - 47 **Cressoni M**, Cadringer P, Chiurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, Bugedo G, Gattinoni L. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014; **189**: 149-158 [PMID: 24261322 DOI: 10.1164/rccm.201308-1567OC]
 - 48 **Rocco PR**, Pelosi P, de Abreu MG. Pros and cons of recruitment maneuvers in acute lung injury and acute respiratory distress syndrome. *Expert Rev Respir Med* 2010; **4**: 479-489 [PMID: 20658909 DOI: 10.1586/ers.10.43]
 - 49 **Stefanidis K**, Dimopoulos S, Tripodaki ES, Vitzilaios K, Politis P, Piperopoulos P, Nanas S. Lung sonography and recruitment in patients with early acute respiratory distress syndrome: a pilot study. *Crit Care* 2011; **15**: R185 [PMID: 21816054]
 - 50 **Bouhemad B**, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. *Am J Respir Crit Care Med* 2011; **183**: 341-347 [PMID: 20851923 DOI: 10.1164/rccm.201003-0369OC]
 - 51 **Tsubo T**, Yatsu Y, Tanabe T, Okawa H, Ishihara H, Matsuki A. Evaluation of density area in dorsal lung region during prone position using transesophageal echocardiography. *Crit Care Med* 2004; **32**: 83-87 [PMID: 14707563 DOI: 10.1097/01.CCM.0000104944.18636.B2]
 - 52 **Muders T**, Luepschen H, Zinserling J, Greschus S, Fimmers R, Guenther U, Buchwald M, Grigutsch D, Leonhardt S, Putensen C, Wrigge H. Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury*. *Crit Care Med* 2012; **40**: 903-911 [PMID: 22202705 DOI: 10.1097/CCM.0b013e318236f452]
 - 53 **Bikker IG**, Leonhardt S, Reis Miranda D, Bakker J, Gommers D. Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent

- parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. *Crit Care* 2010; **14**: R100 [PMID: 20509966 DOI: 10.1186/cc9036]
- 54 **Borges JB**, Costa EL, Suarez-Sipmann F, Widström C, Larsson A, Amato M, Hedenstierna G. Early inflammation mainly affects normally and poorly aerated lung in experimental ventilator-induced lung injury*. *Crit Care Med* 2014; **42**: e279-e287 [PMID: 24448197 DOI: 10.1097/CCM.000000000000161]
 - 55 **Rouby JJ**, Puybasset L, Nieszkowska A, Lu Q. Acute respiratory distress syndrome: lessons from computed tomography of the whole lung. *Crit Care Med* 2003; **31**: S285-S295 [PMID: 12682454 DOI: 10.1097/01.CCM.0000057905.74813.BC]
 - 56 **Constantin JM**, Jaber S, Futier E, Cayot-Constantin S, Verny-Pic M, Jung B, Bailly A, Guerin R, Bazin JE. Respiratory effects of different recruitment maneuvers in acute respiratory distress syndrome. *Crit Care* 2008; **12**: R50 [PMID: 18416847 DOI: 10.1186/cc6869]
 - 57 **Grasso S**, Stripoli T, De Michele M, Bruno F, Moschetta M, Angelelli G, Munno I, Ruggiero V, Anaclerio R, Cafarelli A, Driessen B, Fiore T. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med* 2007; **176**: 761-767 [PMID: 17656676 DOI: 10.1164/rccm.200702-193OC]
 - 58 **Caironi P**, Carlesso E, Cressoni M, Chiumello D, Moerer O, Chiurazzi C, Brioni M, Bottino N, Lazzarini M, Bugedo G, Quintel M, Ranieri VM, Gattinoni L. Lung recruitability is better estimated according to the Berlin definition of acute respiratory distress syndrome at standard 5 cm H₂O rather than higher positive end-expiratory pressure: a retrospective cohort study. *Crit Care Med* 2015; **43**: 781-790 [PMID: 25513785 DOI: 10.1097/CCM.0000000000000770]
 - 59 **Dasenbrook EC**, Needham DM, Brower RG, Fan E. Higher PEEP in patients with acute lung injury: a systematic review and meta-analysis. *Respir Care* 2011; **56**: 568-575 [PMID: 21276322 DOI: 10.4187/respcare.01011rc01011r1dasenbrook]
 - 60 **Grasso S**, Fanelli V, Cafarelli A, Anaclerio R, Amabile M, Ancona G, Fiore T. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; **171**: 1002-1008 [PMID: 15665322 DOI: 10.1164/rccm.200407-940OC]
 - 61 **Slutsky AS**, Hudson LD. PEEP or no PEEP--lung recruitment may be the solution. *N Engl J Med* 2006; **354**: 1839-1841 [PMID: 16641401 DOI: 10.1056/NEJMe068045]
 - 62 **Goligher EC**, Villar J, Slutsky AS. Positive end-expiratory pressure in acute respiratory distress syndrome: when should we turn up the pressure? *Crit Care Med* 2014; **42**: 448-450 [PMID: 24434443 DOI: 10.1097/01.ccm.0000435685.00716.48]
 - 63 **Santa Cruz R**, Rojas JL, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2013; **6**: CD009098 [PMID: 23740697 DOI: 10.1002/14651858.CD009098.pub2]
 - 64 **Lachmann B**. Open up the lung and keep the lung open. *Intensive Care Med* 1992; **18**: 319-321 [PMID: 1469157]
 - 65 **Huh JW**, Jung H, Choi HS, Hong SB, Lim CM, Koh Y. Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. *Crit Care* 2009; **13**: R22 [PMID: 19239703 DOI: 10.1186/cc7725]
 - 66 **Cressoni M**, Chiumello D, Carlesso E, Chiurazzi C, Amini M, Brioni M, Cadringer P, Quintel M, Gattinoni L. Compressive forces and computed tomography-derived positive end-expiratory pressure in acute respiratory distress syndrome. *Anesthesiology* 2014; **121**: 572-581 [PMID: 25050573 DOI: 10.1097/ALN.0000000000000373]
 - 67 **Pintado MC**, de Pablo R, Trascasa M, Milicua JM, Rogero S, Daguerre M, Cambronero JA, Arribas I, Sánchez-García M. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respir Care* 2013; **58**: 1416-1423 [PMID: 23362167 DOI: 10.4187/respcare.02068]
 - 68 **Rodriguez PO**, Esperanza JA, Valentini R. Transpulmonary pressure in acute respiratory distress syndrome. *Crit Care Med* 2013; **41**: e9-10 [PMID: 23269178 DOI: 10.1097/CCM.0b013e318270e569]

P- Reviewer: Inchauspe A **S- Editor:** Tian YL
L- Editor: A **E- Editor:** Liu SQ



Basic Study

***In vivo* analysis of intestinal permeability following hemorrhagic shock**

Tom Alsaigh, Marisol Chang, Michael Richter, Rafi Mazor, Erik B Kistler

Tom Alsaigh, Marisol Chang, Michael Richter, Rafi Mazor, Department of Bioengineering, the Institute of Engineering in Medicine, University of California San Diego, La Jolla, CA 92093-0412, United States

Erik B Kistler, Department of Anesthesiology and Critical Care, VA San Diego Healthcare System, San Diego, CA 92161-5085, United States

Author contributions: Alsaigh T, Chang M, Richter M, Mazor R and Kistler EB were involved in the conception and execution of experiments, data analysis and writing the manuscript; all authors drafted the article and made critical revisions related to the intellectual content of the manuscript and approved the final manuscript.

Supported by Career Development Award (CDA2) 1K2BX-001277-01A1 from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, the Foundation for Anesthesia Education and Research and the American Society of Critical Care Anesthesiologists and NIH GM085072-06.

Institutional review board statement: The animal protocol was reviewed and approved by the Animal Subjects Committee of the University of California, San Diego (A3033-01).

Institutional animal care and use committee statement: The animal protocol was reviewed and approved by the Animal Subjects Committee of the University of California, San Diego (A3033-01) and conforms to the Guide for the Care and Use of Laboratory Animals by the United States National Institutes of Health (NIH Publication No. 85-23, 1996).

Conflict-of-interest statement: To the best of our knowledge, no conflicts of interest exist.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this

work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Erik B Kistler, MD, PhD, Assistant Professor of Anesthesiology and Critical Care, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161-5085, United States. ekistler@ucsd.edu
Telephone: +1-858-5528585-6927
Fax: +1-858-5340104

Received: May 12, 2015
Peer-review started: May 20, 2015
First decision: June 24, 2015
Revised: July 20, 2015
Accepted: August 20, 2015
Article in press: August 21, 2015
Published online: November 4, 2015

Abstract

AIM: To determine the time course of intestinal permeability changes to proteolytically-derived bowel peptides in experimental hemorrhagic shock.

METHODS: We injected fluorescently-conjugated casein protein into the small bowel of anesthetized Wistar rats prior to induction of experimental hemorrhagic shock. These molecules, which fluoresce when proteolytically cleaved, were used as markers for the ability of proteolytically cleaved intestinal products to access the central circulation. Blood was serially sampled to quantify the relative change in concentration of proteolytically-cleaved particles in the systemic circulation. To provide spatial resolution of their location, particles in the mesenteric microvasculature were imaged using *in vivo* intravital fluorescent microscopy. The experiments were then repeated using an alternate measurement technique, fluorescein isothiocyanate

(FITC)-labeled dextrans 20, to semi-quantitatively verify the ability of bowel-derived low-molecular weight molecules (< 20 kD) to access the central circulation.

RESULTS: Results demonstrate a significant increase in systemic permeability to gut-derived peptides within 20 min after induction of hemorrhage (1.11 ± 0.19 vs 0.86 ± 0.07 , $P < 0.05$) compared to control animals. Reperfusion resulted in a second, sustained increase in systemic permeability to gut-derived peptides in hemorrhaged animals compared to controls (1.2 ± 0.18 vs 0.97 ± 0.1 , $P < 0.05$). Intravital microscopy of the mesentery also showed marked accumulation of fluorescent particles in the microcirculation of hemorrhaged animals compared to controls. These results were replicated using FITC dextrans 20 [10.85 ± 6.52 vs 3.38 ± 1.11 fluorescent intensity units ($\times 10^5$, $P < 0.05$, hemorrhagic shock vs controls)], confirming that small bowel ischemia in response to experimental hemorrhagic shock results in marked and early increases in gut membrane permeability.

CONCLUSION: Increased small bowel permeability in hemorrhagic shock may allow for systemic absorption of otherwise retained proteolytically-generated peptides, with consequent hemodynamic instability and remote organ failure.

Key words: Small bowel ischemia; Hemorrhagic shock; Peptides; Microcirculation; Proteolysis

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Although the concept of systemically circulating molecules from the bowel in response to shock is not new (*e.g.*, bacterial “translocation”), the premise that small, proteolytically-derived molecules transit the bowel early in shock has not previously been examined. We offer evidence that proteolytically-derived peptides formed in the gut reach the systemic circulation in experimental hemorrhagic shock. The time-course and spatial disposition of low-molecular weight peptides *in vivo* was examined using real-time fluorescent intravital microscopy of the microcirculation and systemically as a first step towards demonstrating a pivotal role that these factors may play in affecting hemodynamic instability in early shock.

Alsaigh T, Chang M, Richter M, Mazor R, Kistler EB. *In vivo* analysis of intestinal permeability following hemorrhagic shock. *World J Crit Care Med* 2015; 4(4): 287-295 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v4/i4/287.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v4.i4.287>

INTRODUCTION

The small intestinal mucosa normally serves as a

selective barrier to uncontrolled transport of large-molecular weight bowel contents into the systemic circulation, while simultaneously allowing the absorption of low-molecular weight nutrients necessary to sustain life. Severe hemorrhagic shock leads to decreased organ perfusion, especially to the bowel. Resultant ischemia to the gut adversely affects its function, and in particular the ability of the small bowel to act as a selective barrier to the uncontrolled egress of luminal molecules into the systemic circulation. It has previously been shown that destruction of the small gut luminal surface occurs very early in shock, and that this destruction appears to be mediated by enzymatic (proteolytic) activity at the bowel mucosa^[1,2]. Under normal circumstances the bowel is protected from enzymatic degradation by a proteolytically-impermeant mucus layer. Maintenance of this layer requires ATP, and the ability of the protective mucus layer to prevent digestive enzyme attack of the mucosal wall is degraded with ischemia^[3]. With the mucus layer compromised in shock, digestive enzymes in the bowel are able to destroy the underlying enterocyte layer, cell-cell junctions and the serosa, leading to increases in bowel permeability^[1].

Enteral infusion of (serine) protease inhibitors into the small bowel lumen has been shown to be protective in multiple forms of experimental circulatory shock that result in gut ischemia, including hemorrhagic, endotoxic, and peritonitis shock^[4]. Infusion of protease inhibitors enterally (but not systemically^[5]) prevents or mitigates mortality in different species^[6] after shock, including man^[7], presumably by decreasing permeability of the small bowel to inflammatory mediators that otherwise cause systemic inflammation and multiple organ failure^[8]. However, the mechanisms by which the mitigation of bowel injury improves outcomes after shock are largely unexplored.

Hemorrhagic shock has been reported to increase intestinal permeability, but this has largely been studied *ex-vivo* (*e.g.*, Ussing chambers^[9]) or using small markers such as radio-labeled sugars^[10] or at single or later time points^[11,12]. As such, the time-course and the extent of bowel permeability changes in this condition are largely unexplored. We hypothesized that proteolytically-derived peptides may be among the earliest mediators to cross the bowel mucosal barrier in shock and sought to determine their time-course *in vivo*, in order to further delineate the role and timing of bowel-mediated inflammation and remote organ injury in hemorrhagic shock.

MATERIALS AND METHODS

Ethics statement

The animal protocol was reviewed and approved by the University of California, San Diego Institutional Animal Care and Use Committee and conforms to the Guide for the Care and Use of Laboratory Animals by the United States National Institutes of Health (NIH Publication No.

85-23, 1996).

Animals and surgical procedure

Eight-week-old non-fasted male Wistar rats (300-350 g, Charles River Breeding Laboratories, Wilmington, Mass) were randomly assigned to either hemorrhagic shock ($n = 11$) or sham shock control groups ($n = 11$). The animal protocol was designed to minimize pain or discomfort to the animals. The animals were acclimatized to laboratory conditions (23 °C, 12 h/12 h light/dark, 50% humidity, ad libitum access to food and water) for over one week prior to experimentation. Animals were not fasted before experiments.

Animals were anesthetized (pentobarbital sodium, Abbott Laboratories, North Chicago, IL, 50 mg/kg, *im*) and the left femoral vein and artery were cannulated to facilitate continuous cardiovascular monitoring and blood withdrawal for the experimental procedure. Further pentobarbital was given intravenous (*iv*) as necessary to maintain adequate anesthetic plane. Heparin was given (10 U/mL *iv*) to facilitate exsanguination and prevent clotting in all animals. The animals breathed spontaneously without tracheotomy.

Shock protocol

Hemorrhagic shock was induced by careful removal of blood *via* the femoral vein in 1 mL aliquots until a mean arterial pressure (MAP) of 35 mmHg was achieved. The MAP was maintained at 35 mmHg for 100 min, at which time shed blood was re-warmed to 37 °C and slowly reinfused in 1 mL aliquots, analogous to blood withdrawal, *via* the femoral vein. Animals were then observed for 100 min (Reperfusion) before termination of the experiment (Beuthanasia®, 0.22 mL/kg, *iv*). This model of hemorrhagic shock has previously been shown to result in ischemia-mediated damage to the small bowel^[2,4]. Sham-shock animals were instrumented and manipulated as above without hemorrhage as the comparator group.

Fluorophore-coupled casein injection into the small bowel

To determine the ability of bowel-generated proteolytically-cleaved peptides to diffuse into the central circulation, fluorescently-labeled casein (EnzChek Protease Assay kit, red-fluorescent BODIPY® TR-X, Invitrogen, Life Technologies, Grand Island, NY) was injected into the small bowel before the shock procedure ($n = 6$, both shock and sham shock control groups). The casein is labeled with multiple fluorophores and only fluoresces upon proteolytic cleavage. In confirmatory separate experiments, and because the molecular weight of the fluorescent casein-derived peptides was unknown, fluorescein isothiocyanate (FITC)-dextran 20 (Sigma, St Louis), as a known molecular weight marker (20 kD MW) was substituted for the fluorescently-labeled casein ($n = 5$, both shock and sham shock control groups). Before induction of hemorrhagic shock (or

analogous time period in the sham-shock control group) a midline incision was made and the small intestine was carefully exteriorized from the abdomen onto moist warmed (37 °C) gauze. Either one mL casein solution or FITC-dextran 20 was injected sequentially along the length of the small bowel from the cecum proximally to the duodenum (10 mL of fluorescent solution total).

In vivo intravital fluorescent imaging of the rat mesentery

The rat mesentery was gently exposed and draped over a transparent pedestal on a heated animal stage (at 37 °C) as previously described^[13]. The mesentery preparation was continuously superfused (2.0 mL/min) with Krebs-Henseleit solution (37 °C) containing a 95% N₂-5% CO₂ gas mixture, with care taken to maintain adequate fluid superfusion of the tissue. The mesenteric microcirculation was imaged using an intravital microscope [water immersion objective lens ($\times 25$, numerical aperture = 0.60, Leitz; Wetzlar, Germany)] by a color charge-coupled device camera (DEI-470, Optronics Engineering; Goleta, CA; frame rate 1/125 s for bright field and 1/2 s for fluorescence light). All images were recorded (Model AG-a270P, Panasonic; Tokyo, Japan) and digitally stored for analysis. Fluorescent images were elicited using a 200-W mercury lamp. The light was passed through a quartz collector, heat filter (KG-2, Zeiss; Oberkochen, Germany), and fluorescent filter set (Excitation/Emission: 590/625 nm for casein peptide-derived fluorescence, Excitation/Emission: 485/535 nm for FITC dextran-20 fluorescence (in separate experiments), L3 filter cube, Ploem Pak, Leitz). Single microscopic fields (approximately 300 μ m \times 350 μ m) containing arterioles and venules were examined. Wright's stain was used to identify the presence of inflammatory cell types. Briefly, mesentery sectors were excised, fixed in cold acetone (10 min) and subsequently stained with Wright's stain (1 min). Slides were washed, dehydrated and cover-slipped for imaging.

Plasma and organ fluorescence assay

After injection of fluorescent casein into the lumen of the small intestine, blood (50 μ L) from the femoral artery was collected every 20 min for the duration of the experiment (200 min total) and plasma fluorescence was read immediately (SpectraMax Gemini XS, Molecular Devices, Sunnyvale, CA). In animals injected with FITC-dextran 20, plasma was collected before the shock period and at reperfusion. At the end of the experiments heart, liver and lungs were collected, homogenized and fluorescence readings were performed to determine casein-derived peptide concentrations in these organs.

Statistical analysis

Results are presented as mean \pm SD, where applicable. Unpaired comparisons of means between two groups in time were carried out using Repeated Measures ANOVA or two-tailed Student's *t*-test where appropriate;

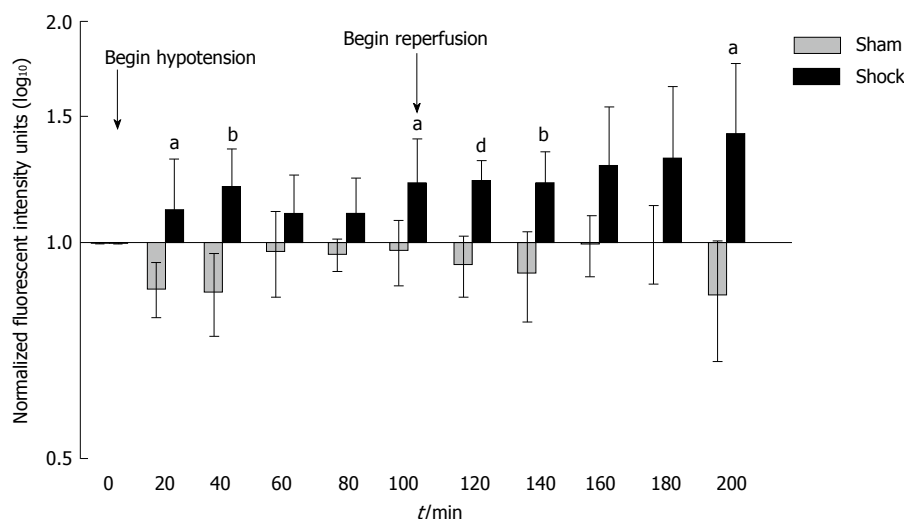


Figure 1 Increased bowel permeability to casein peptides after hemorrhagic shock. Small bowel permeability as measured by systemic concentrations of proteolytically-generated peptides from fluorescently labelled casein injected into the small bowel. Note the early increase in bowel permeability at 20 min, followed by a second, sustained increase in bowel permeability at reperfusion. Values normalized to background fluorescent levels in the systemic circulation at time T = 0 and plotted as log₁₀ concentrations. Results reported as Mean ± SD. ^a*P* < 0.05, ^b*P* < 0.01, ^d*P* < 0.001 using Repeated Measures ANOVA for hemorrhagic shock (*n* = 6) vs sham-shock control (*n* = 6) groups at each time point.

comparisons between measurements in the same group were conducted using two-tailed Student's paired *t*-test. Because of significant differences between pre-ischemic values in the (plasma) casein-derived peptide experiments data were normalized prior to conducting statistical comparisons. *P* < 0.05 was considered to be significant.

RESULTS

Concentrations of fluorescent casein-derived peptides increase in the plasma of shocked animals in a time-dependent fashion

Hemorrhagic shock (average volume of blood withdrawn and subsequently reperfused: 6.6 ± 2.9 mL) led to time-dependent increases in small bowel permeability compared to that of sham-shock control animals as measured by increases in bowel-derived proteolytically-generated peptide fluorescence in the central circulation (Figure 1). A significant increase in small bowel permeability was apparent by as early as 20 min (*P* < 0.05 compared to the sham-shock control group), and was followed by a second and sustained increase in measured permeability upon reperfusion of shed blood (*P* < 0.05 and 0.01 compared to the sham-shock control group).

Fluorescence-conjugated casein peptides enter the systemic circulation and circulate in the mesentery tissue and microvasculature

Co-incident with increased plasma concentrations in shock animals, the number of fluorescently-conjugated casein-derived peptides was substantially greater in the parenchyma and microvasculature of the mesentery of shocked animals (*n* = 6) compared to their non-shocked

controls (*n* = 6) (Figure 2). Of note, there appeared to be extensive co-localization of casein-derived peptides with white blood cells in the microcirculation (Figure 3), suggesting that some of these casein-derived peptides may be inflammatory. In order to quantify the increases in bowel permeability to small molecular-weight molecules, in confirmatory experiments the larger FITC-dextran 20 (molecular weight approximately 20 kD) tracer was injected into the small bowel instead of fluorescent casein at the initiation of the experimental procedures. These results demonstrate a significant increase in measured FITC fluorescence in the plasma of shocked animals (*n* = 5) compared to sham-shock controls (*n* = 5) after reperfusion [10.85 ± 6.52 vs 3.38 ± 1.11 fluorescent intensity units ($\times 10^5$, *P* < 0.05)]. There were also significant increases in permeability-mediated FITC fluorescence after 100 min reperfusion compared to initial values in both shocked animals (10.85 ± 6.52 vs 3.97 ± 4.52 , $\times 10^5$, *P* < 0.05, *n* = 5) and controls (3.38 ± 1.11 vs 1.44 ± 0.64 , $\times 10^5$, *P* < 0.05, *n* = 5) (Figure 4). Intravital microscopy of the rat mesentery confirmed increases in microvascular permeability to FITC-dextran 20 after hemorrhagic shock (Figure 5). However, less extravasation of FITC-dextran 20 into the surrounding tissues was observed compared to that seen with casein-derived peptides, suggesting a possible differential increase in vascular permeability to the larger FITC-dextran 20 molecule. Fluorescence of casein-derived peptides in remote tissues (*n* = 4 for both groups) displayed no significant differences in heart tissue (3210.7 ± 493.8 vs 2406.2 ± 841.8 , *P* = 0.15) liver (4124.6 ± 1193.2 vs 6234.8 ± 1894.4 , *P* = 0.11), and lung (2860.4 ± 1149.6 vs 3055.8 ± 1117.8 , *P* = 0.81) in the shock group compared to sham-shock controls.

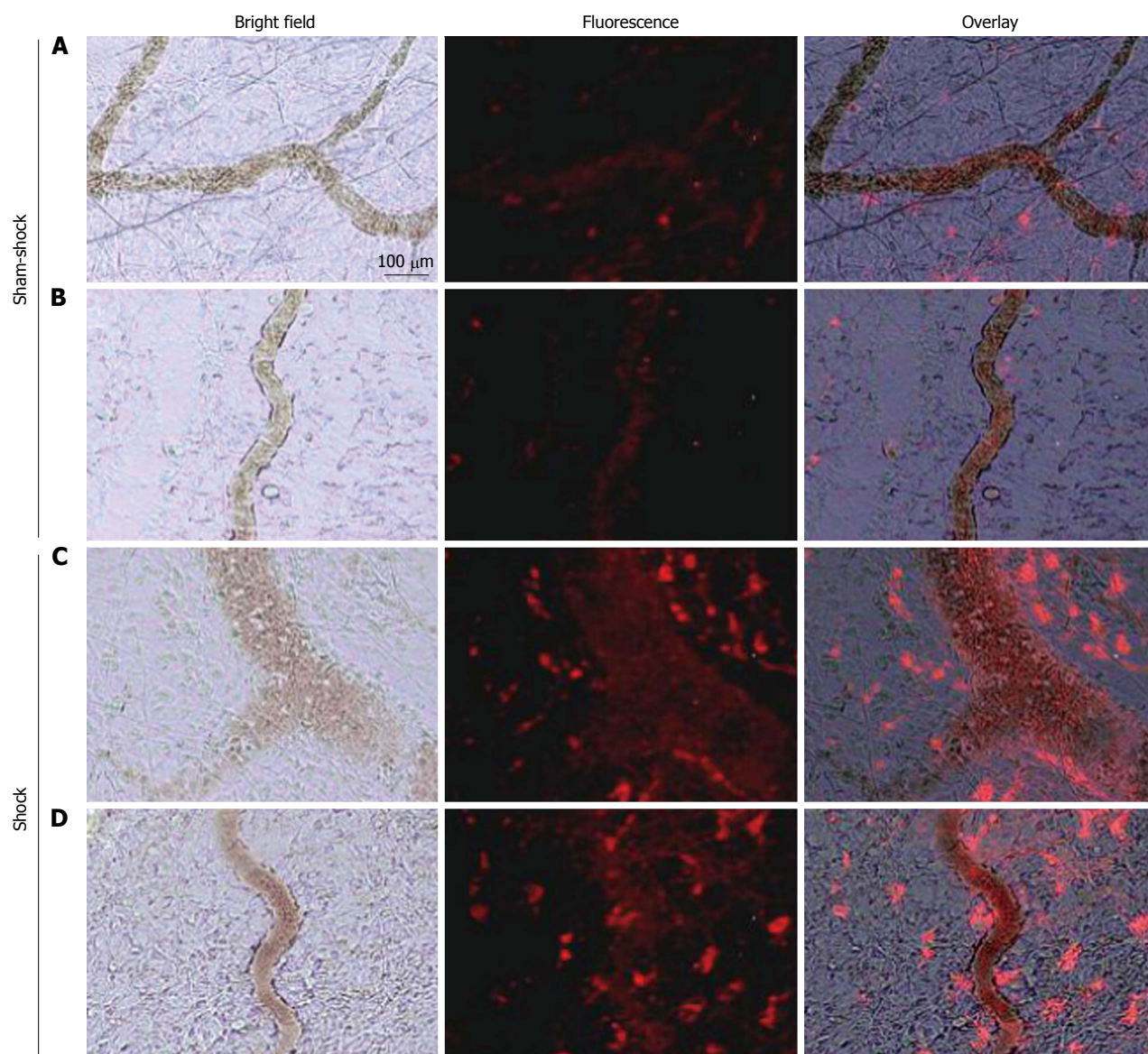


Figure 2 Selected *in vivo* microvascular images from two different sham-shock control (A and B) and shock (C and D) animals ($n = 6$, both groups) after hemorrhagic shock or sham-shock and reperfusion. Note the significantly higher levels of red fluorescent casein-derived peptides in the microvasculature and within the interstitium in shock animals (C and D) compared with their sham shock counterparts (A and B).

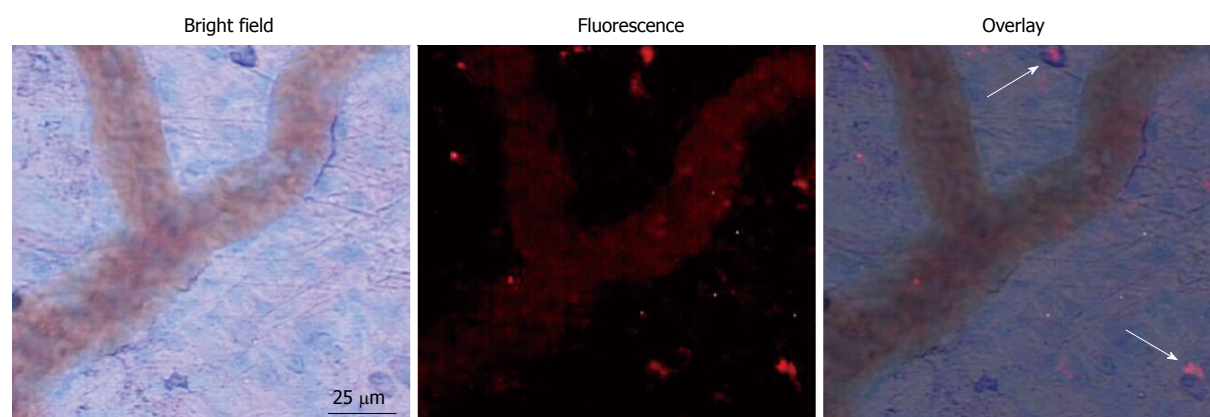


Figure 3 Representative micrograph with overlays depicting infiltration of white blood cells into the mesentery following shock. Arrows indicate co-localization of fluorescent casein-derived peptide with white blood cells, suggesting a possible inflammatory component to the casein-derived peptides.

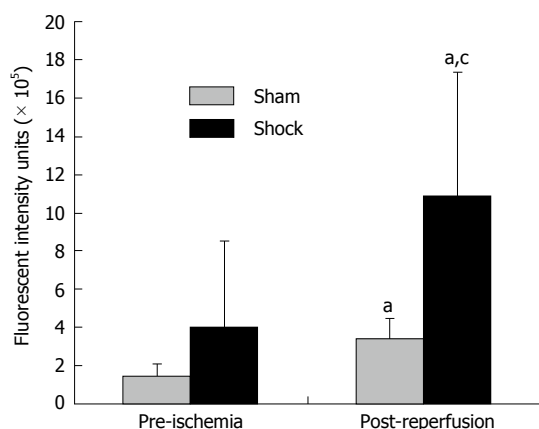


Figure 4 Increased bowel permeability after fluorescein isothiocyanate-Dextran-20 after hemorrhagic shock. Small bowel permeability after experimental hemorrhagic shock as measured by systemic concentrations of FITC-Dextran-20 injected into the bowel. ^a $P < 0.05$ post-reperfusion vs initial values using two-tailed paired Student's *t*-test, ^c $P < 0.05$ shock group ($n = 5$) vs sham-shock controls ($n = 5$) using two-tailed unpaired Student's *t*-test.

DISCUSSION

It has become increasingly apparent that fulminate circulatory shock, regardless of origin, results in small bowel ischemia^[4]. Likewise, there is increasing evidence to suggest that prevention of bowel ischemia is beneficial to the organism, and preventing proteolytic digestion of the bowel mucosa, arising as a consequence of bowel ischemia, leads to improved outcomes in experimental shock^[3,14,15]. The mechanisms by which bowel ischemia results in multiorgan failure and shock, are however, incompletely understood. It has long been hypothesized that "translocation" of bacterial product from the bowel to the systemic circulation contributes to deleterious outcomes in shock^[16,17], but data supporting this theory are sparse and contradictory^[10,18]. More importantly, there has been very little progress from a clinical perspective in attempting to modify or mitigate bacterial "translocation", which lessens enthusiasm for this approach^[19].

Alternatively, bowel ischemia, as we demonstrate here in response to experimental hemorrhagic shock of non-gastrointestinal origin, leads to very early increases in microvascular permeability to relatively low molecular weight products from the lumen of the bowel into the systemic circulation. Gut-derived peptides lie on a continuum from approximately 0.1-10 kD, several orders of magnitude smaller than bacteria and their generated inflammatory products^[20], and can be found in a myriad number of forms and configurations. Therefore, it is reasonable to suggest that gut-derived peptides are among the first molecules from the bowel to enter the central circulation and subsequently reach remote organs. That many of these peptides have vasoactive and/or inflammatory potential is well-established, including peptides derived from casein^[21,22].

We propose that some of the initial inflammatory mediators that circulate systemically in early experimental hemorrhagic shock are gut-derived proteo-

lytically-generated peptides. Although increased bowel permeability in response to shock and other stressors has been well-documented as a general concept^[23] and to fixed molecular weight tracers^[24], we demonstrate here under real-time *in vivo* observation that in experimental hemorrhagic shock there is a significant increase in small bowel permeability compared to sham-shock control animals within 20 min of ischemia to proteolytically generated peptide products from the gut, implicating bowel compromise as an early and perhaps inciting event in this model. The rapid increase in measured bowel permeability during early ischemia occurs during a low-perfusion state with concomitant limited flux of fluorescently-labelled peptides, implying an under-estimation of the permeability changes occurring at the bowel mucosa at this time. Conversely, sustained increases in small bowel permeability measured after blood reperfusion, where there is increased flux and possible "wash-out" of fluorescent tracer, may represent an over-estimation of increased bowel permeability rather than a second "reperfusion" injury.

An interesting observation from the study was the noticeable and frequent co-localization of casein-derived peptide fragments with possible inflammatory cells (mast cells vs macrophages, etc.). Although inflammatory activity of casein-derived peptides has previously been reported, this has not been directly confirmed *in vivo*^[25-27]. Further investigation is necessary to confirm the robustness and clinical relevance of these findings, as fluorescently-labelled casein and FITC-dextran 20 were used as markers of permeability and not for assessment of their intrinsic biologic activities. It is appreciated that there are limitations to the use of fluorescently-labelled markers when assessing permeability; it was for this reason that we chose to study small-molecule permeability using two different markers^[28].

There are several limitations to this study. Among these includes our inability to categorize precisely the molecular weights of the fluorescently-bound casein-derived peptides secondary to the extreme heterogeneity of the cleavage products and the non-linear distribution of the fluorophores on the parent protein. However, it can be reasonably inferred that the MW's of these fluorescent compounds are between 0.1-10 kD, (parent compound MW: 19-25 kD) and smaller than native casein^[29]. Previous studies indicate that these peptides are produced in the bowel rather than proteolytically generated in the circulation after becoming systemic^[3,30,31]. Although there is a lack of ancillary temporal data correlating *in vivo* effects with increases in permeability, confirmatory measurements using FITC-dextran 20 support the assertion that *in vivo* permeability to larger molecular-weight particles also increases to some extent in shock^[23,24]. Further studies using calibrated tracers at discrete time-points and anatomic locations are necessary to completely quantify these findings. Heparin given systemically before experimental hemorrhage is a possible confounder to our

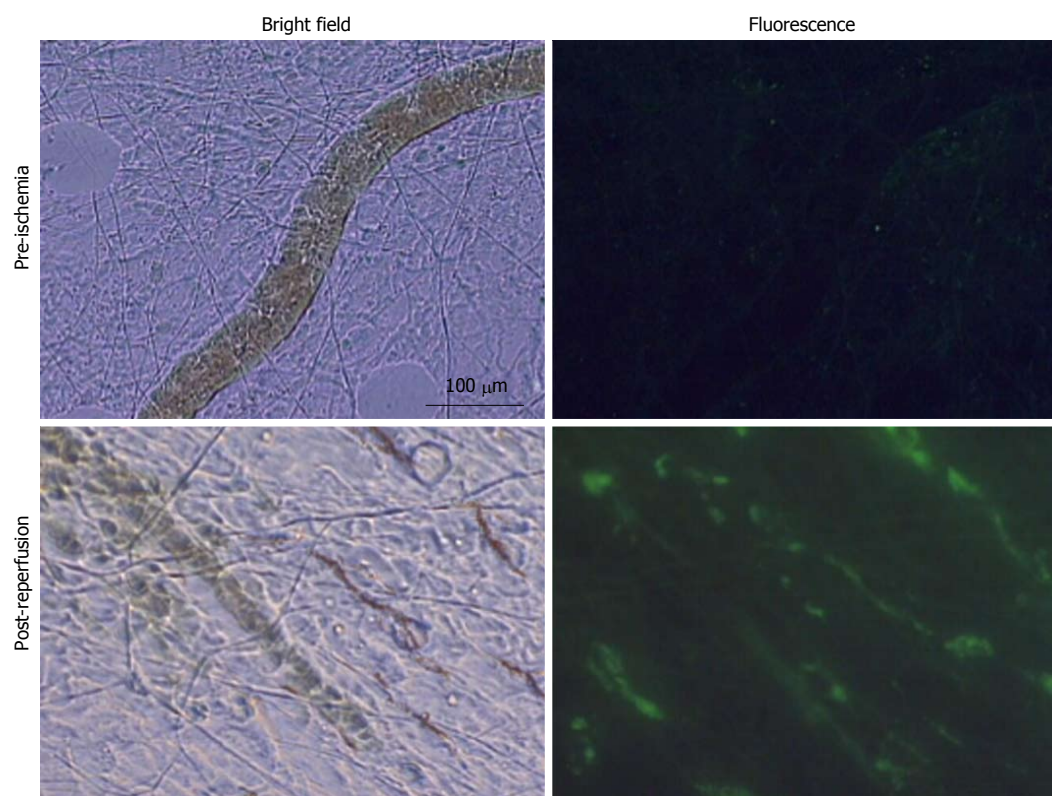


Figure 5 Selected *in vivo* microvascular images of the mesentery from a shock animal pre-ischemia and 100 min post-reperfusion ($n = 5$). Note the significantly higher levels of fluorescein isothiocyanate-dextran-20 in the microvasculature vs initial values and the relative lack of flow after reperfusion.

results when the coagulopathy of hemorrhage/trauma is considered. This is an unavoidable aspect of our hemorrhage model in which blood otherwise clots the catheters and while stored during the ischemic period. An unanticipated result was the heterogeneous accumulation of the fluorescently-labelled peptides in remote tissues. Because of the marked increase in fluorescently-labelled peptides in the mesentery and systemic circulation of animals exposed to experimental hemorrhagic shock compared to sham shock controls it was anticipated that remote tissues would demonstrate similar increases in gut-derived peptide concentrations after shock. The reasons for this lack of difference are unclear but could be due to preferential absorption in other non-measured tissues, heterogeneous accumulation in the selected organs, or simply minimal measured peptide uptake relative to organ tissue mass. Finally, it is acknowledged that the definition of "permeability" as used in these studies is semi-quantitative, in that what is measured is the resulting accumulation of tracer in the measured (vascular or tissue) compartment. As all variables except the changes in permeability are held constant between groups, the permeability results presented here are, strictly speaking, a ratio of permeability changes between the control and shock groups and as such are necessarily semi-quantitative^[32].

In conclusion, this study demonstrates that early increases in small bowel permeability occur during experimental hemorrhagic shock and that proteolytically-derived peptides may be the defining molecules that

instigate early inflammation and hemodynamic compromise. Further studies are needed to determine precisely the identity of these putative gut-derived inflammatory mediators and their origin, as well as strategies for preventing their egress into the systemic circulation.

COMMENTS

Background

Ischemia resulting from acute hemorrhage compromises the intestinal barrier, leading to increased permeability of the membrane to bowel-derived contents. Some of these molecules may be intrinsically inflammatory and may possibly contribute to the organ dysfunction and mortality seen in shock.

Research frontiers

The ability of intestinal products, particularly those that are proteolytically generated, to escape into the central circulation following acute blood loss and their subsequent fate is not well understood. The authors were interested in determining *in vivo* the time course and the extent to which these particles access the central circulation following hemorrhagic shock.

Innovations and breakthroughs

The authors demonstrate in this manuscript that early increases in small bowel permeability occur very early during experimental hemorrhagic shock.

Applications

Proteolytically-derived peptides from the bowel enter the systemic circulation early in shock and may be defining molecules that instigate early inflammation and hemodynamic compromise in shock and associated poor bowel perfusion states.

Peer-review

This is a well written study investigating intestinal permeability after shock in a

rodent model.

REFERENCES

- 1 **Chang M**, Alsaigh T, Kistler EB, Schmid-Schönbein GW. Breakdown of mucin as barrier to digestive enzymes in the ischemic rat small intestine. *PLoS One* 2012; **7**: e40087 [PMID: 22768227 DOI: 10.1371/journal.pone.0040087]
- 2 **Chang M**, Kistler EB, Schmid-Schönbein GW. Disruption of the mucosal barrier during gut ischemia allows entry of digestive enzymes into the intestinal wall. *Shock* 2012; **37**: 297-305 [PMID: 22089198 DOI: 10.1097/SHK.0b013e318240b59b]
- 3 **Kistler EB**, Alsaigh T, Chang M, Schmid-Schönbein GW. Impaired small-bowel barrier integrity in the presence of luminal pancreatic digestive enzymes leads to circulatory shock. *Shock* 2012; **38**: 262-267 [PMID: 22576000 DOI: 10.1097/SHK.0b013e31825b1717]
- 4 **DeLano FA**, Hoyt DB, Schmid-Schönbein GW. Pancreatic digestive enzyme blockade in the intestine increases survival after experimental shock. *Sci Transl Med* 2013; **5**: 169ra11 [PMID: 23345609 DOI: 10.1126/scitranslmed.3005046]
- 5 **Kistler EB**, Lefer AM, Hugli TE, Schmid-Schönbein GW. Plasma activation during splanchnic arterial occlusion shock. *Shock* 2000; **14**: 30-34 [PMID: 10909890]
- 6 **Kim HD**, Malinoski DJ, Borazjani B, Patel MS, Chen J, Slone J, Nguyen XM, Steward E, Schmid-Schönbein GW, Hoyt DB. Inhibition of intraluminal pancreatic enzymes with nafamostat mesilate improves clinical outcomes after hemorrhagic shock in swine. *J Trauma* 2010; **68**: 1078-1083 [PMID: 20453762 DOI: 10.1097/TA.0b013e3181da78b1]
- 7 **Lee YT**, Wei J, Chuang YC, Chang CY, Chen IC, Weng CF, Schmid-Schönbein GW. Successful treatment with continuous enteral protease inhibitor in a patient with severe septic shock. *Transplant Proc* 2012; **44**: 817-819 [PMID: 22483504 DOI: 10.1016/j.transproceed.2012.03.032]
- 8 **Doucet JJ**, Hoyt DB, Coimbra R, Schmid-Schönbein GW, Junger WG, Paul L W, Loomis WH, Hugli TE. Inhibition of enteral enzymes by enteroclysis with nafamostat mesilate reduces neutrophil activation and transfusion requirements after hemorrhagic shock. *J Trauma* 2004; **56**: 501-510; discussion 510-511 [PMID: 15128119]
- 9 **Deitch EA**, Senthil M, Brown M, Caputo F, Watkins A, Anjaria D, Badami C, Pisarenko V, Doucet D, Lu Q, Feketeova E, Xu DZ. Trauma-shock-induced gut injury and the production of biologically active intestinal lymph is abrogated by castration in a large animal porcine model. *Shock* 2008; **30**: 135-141 [PMID: 18180696 DOI: 10.1097/shk.0b013e318161724f]
- 10 **Schlichting E**, Grotmol T, Kähler H, Naess O, Steinbakk M, Lyberg T. Alterations in mucosal morphology and permeability, but no bacterial or endotoxin translocation takes place after intestinal ischemia and early reperfusion in pigs. *Shock* 1995; **3**: 116-124 [PMID: 7749938]
- 11 **Du MH**, Luo HM, Hu S, Lv Y, Lin ZL, Ma L. Electroacupuncture improves gut barrier dysfunction in prolonged hemorrhagic shock rats through vagus anti-inflammatory mechanism. *World J Gastroenterol* 2013; **19**: 5988-5999 [PMID: 24106399 DOI: 10.3748/wjg.v19.i36.5988]
- 12 **Deitch EA**, Morrison J, Berg R, Specian RD. Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotic-decontaminated rats. *Crit Care Med* 1990; **18**: 529-536 [PMID: 2328600]
- 13 **Kistler EB**, Hugli TE, Schmid-Schönbein GW. The pancreas as a source of cardiovascular cell activating factors. *Microcirculation* 2000; **7**: 183-192 [PMID: 10901497 DOI: 10.1111/j.1549-8719.2000.tb00119.x]
- 14 **Mitsuoka H**, Kistler EB, Schmid-Schönbein GW. Generation of in vivo activating factors in the ischemic intestine by pancreatic enzymes. *Proc Natl Acad Sci USA* 2000; **97**: 1772-1777 [PMID: 10677533]
- 15 **Mitsuoka H**, Kistler EB, Schmid-Schönbein GW. Protease inhibition in the intestinal lumen: attenuation of systemic inflammation and early indicators of multiple organ failure in shock. *Shock* 2002; **17**: 205-209 [PMID: 11900339]
- 16 **Leaphart CL**, Tepas JJ. The gut is a motor of organ system dysfunction. *Surgery* 2007; **141**: 563-569 [PMID: 17462455]
- 17 **Ravin HA**, Rowley D, Jenkins C, Fine J. On the absorption of bacterial endotoxin from the gastro-intestinal tract of the normal and shocked animal. *J Exp Med* 1960; **112**: 783-792 [PMID: 13739891]
- 18 **Yang R**, Gallo DJ, Baust JJ, Watkins SK, Delude RL, Fink MP. Effect of hemorrhagic shock on gut barrier function and expression of stress-related genes in normal and gnotobiotic mice. *Am J Physiol Regul Integr Comp Physiol* 2002; **283**: R1263-R1274 [PMID: 12376421 DOI: 10.1152/ajpregu.00278.2002]
- 19 **Bennett-Guerrero E**, Grocott HP, Levy JH, Stierer KA, Hogue CW, Cheung AT, Newman MF, Carter AA, Rossignol DP, Collard CD. A phase II, double-blind, placebo-controlled, ascending-dose study of Eritoran (E5564), a lipid A antagonist, in patients undergoing cardiac surgery with cardiopulmonary bypass. *Anesth Analg* 2007; **104**: 378-383 [PMID: 17242095 DOI: 10.1213/01.ane.0000253501.07183.2a]
- 20 **Gillis M**, De Ley J, De Cleene M. The determination of molecular weight of bacterial genome DNA from renaturation rates. *Eur J Biochem* 1970; **12**: 143-153 [PMID: 4984994]
- 21 **Kitazawa H**, Yonezawa K, Tohno M, Shimamoto T, Kawai Y, Saito T, Wang JM. Enzymatic digestion of the milk protein beta-casein releases potent chemotactic peptide(s) for monocytes and macrophages. *Int Immunopharmacol* 2007; **7**: 1150-1159 [PMID: 17630193 DOI: 10.1016/j.intimp.2007.04.008]
- 22 **Abdelhamid AE**, Chuang SL, Hayes P, Fell JM. Evolution of in vitro cow's milk protein-specific inflammatory and regulatory cytokine responses in preterm infants with necrotising enterocolitis. *J Pediatr Gastroenterol Nutr* 2013; **56**: 5-11 [PMID: 22903007 DOI: 10.1097/MPG.0b013e31826ee9ec]
- 23 **Kuebler JF**, Toth B, Rue LW, Bland KI, Chaudry IH. Differential alterations in intestinal permeability after trauma-hemorrhage. *J Surg Res* 2003; **112**: 198-204 [PMID: 12888338]
- 24 **Russell DH**, Barreto JC, Klemm K, Miller TA. Hemorrhagic shock increases gut macromolecular permeability in the rat. *Shock* 1995; **4**: 50-55 [PMID: 7552778]
- 25 **Takano-Ishikawa Y**, Goto M, Yamaki K. Analysis of leukocyte rolling and migration--using inhibitors in the undisturbed microcirculation of the rat mesentery--on inflammatory stimulation. *Mediators Inflamm* 2004; **13**: 33-37 [PMID: 15203563 DOI: 10.1080/09629350410001664761]
- 26 **Kazlauskaitė J**, Biziulevičius GA, Zukaite V, Biziulevičienė G, Miliukienė V, Siaurys A. Oral tryptic casein hydrolysate enhances phagocytosis by mouse peritoneal and blood phagocytic cells but fails to prevent induced inflammation. *Int Immunopharmacol* 2005; **5**: 1936-1944 [PMID: 16275628 DOI: 10.1016/j.intimp.2005.06.015]
- 27 **Rzodkiewicz P**, Wojtecka-Lukasik E, Szukiewicz D, Schunack W, Maslinski S. Antihistaminic drugs modify casein-induced inflammation in the rat. *Inflamm Res* 2010; **59** Suppl 2: S187-S188 [PMID: 20012883 DOI: 10.1007/s00011-009-0124-5]
- 28 **Rumbaut RE**, Harris NR, Sial AJ, Huxley VH, Granger DN. Leakage responses to L-NAME differ with the fluorescent dye used to label albumin. *Am J Physiol* 1999; **276**: H333-H339 [PMID: 9887048]
- 29 **Fleminger G**, Ragonés H, Merin U, Silanikove N, Leitner G. Low molecular mass peptides generated by hydrolysis of casein impair rennet coagulation of milk. *Int Dairy J* 2013; **30**: 74-78
- 30 **Altshuler AE**, Penn AH, Yang JA, Kim GR, Schmid-Schönbein GW. Protease activity increases in plasma, peritoneal fluid, and vital organs after hemorrhagic shock in rats. *PLoS One* 2012; **7**: e32672 [PMID: 22479334 DOI: 10.1371/journal.pone.0032672]
- 31 **Altshuler AE**, Richter MD, Modestino AE, Penn AH, Heller MJ, Schmid-Schönbein GW. Removal of luminal content protects the small intestine during hemorrhagic shock but is not sufficient

to prevent lung injury. *Physiol Rep* 2013; **1**: e00109 [PMID: 24303180 DOI: 10.1002/phy2.109]

32 **Nagy JA**, Benjamin L, Zeng H, Dvorak AM, Dvorak HF. Vascular

permeability, vascular hyperpermeability and angiogenesis. *Angiogenesis* 2008; **11**: 109-119 [PMID: 18293091 DOI: 10.1007/s10456-008-9099-z]

P- Reviewer: Esmat S, Rahbar E, Santos-Antunes J
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Liu SQ



Retrospective Study

Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury

Kristine H O'Phelan, Amedeo Merenda, Katherine G Denny, Kassandra E Zaila, Cynthia Gonzalez

Kristine H O'Phelan, Amedeo Merenda, Departments of Neurology and Neurosurgery, University of Miami, Miami, FL 33136, United States

Katherine G Denny, Department of Neurology, University of California Davis, Sacramento, CA 95817, United States

Kassandra E Zaila, Hamilton College, Clinton, NY 13323, United States

Cynthia Gonzalez, Division of Neurocritical Care, University of California San Diego, La Jolla, CA 92093-0662, United States

Author contributions: O'Phelan KH and Gonzalez C designed the research; Zaila KE and Gonzalez C performed the research; Denny KG performed the statistical analysis; O'Phelan KH and Merenda A wrote the paper.

Institutional review board statement: This study was reviewed and approved by the IRB (institutional review board) for the University of Miami and the Jackson Memorial Hospital.

Informed consent statement: Informed consent was waived due to negligible risk of harm and the significant importance of evaluating a complete data set. All personal identifiers were removed prior to analysis.

Conflict-of-interest statement: None of the authors have any conflicts of interests. This work was performed without funding.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at kophelan@med.miami.edu.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

[licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)

Correspondence to: Kristine H O'Phelan, MD, Associate Professor of Clinical Neurology, Departments of Neurology and Neurosurgery, University of Miami, 1120 NW 14th St, Miami, FL 33136, United States. kophelan@med.miami.edu
Telephone: +1-305-2434621
Fax: +1-305-2437081

Received: May 14, 2015

Peer-review started: May 14, 2015

First decision: June 24, 2015

Revised: July 8, 2015

Accepted: August 4, 2015

Article in press: August 7, 2015

Published online: November 4, 2015

Abstract

AIM: To examine complications associated with the use of therapeutic temperature modulation (mild hypothermia and normothermia) in patients with severe traumatic brain injury (TBI).

METHODS: One hundred and fourteen charts were reviewed. Inclusion criteria were: severe TBI with Glasgow Coma Scale (GCS) < 9, intensive care unit (ICU) stay > 24 h and non-penetrating TBI. Patients were divided into two cohorts: the treatment group received therapeutic temperature modulation (TTM) with continuous surface cooling and indwelling bladder temperature probes. The control group received standard treatment with intermittent acetaminophen for fever. Information regarding complications during the time in the ICU was collected as follows: Pneumonia was identified using a combination of clinical and laboratory data. Pulmonary embolism, pneumothorax and deep venous thrombosis were identified based on

imaging results. Cardiac arrhythmias and renal failure were extracted from the clinical documentation. acute respiratory distress syndrome and acute lung injury were determined based on chest imaging and arterial blood gas results. A logistic regression was conducted to predict hospital mortality and a multiple regression was used to assess number and type of clinical complications.

RESULTS: One hundred and fourteen patients were included in the analysis (mean age = 41.4, SD = 19.1, 93 males), admitted to the Jackson Memorial Hospital Neuroscience ICU and Ryder Trauma Center (mean GCS = 4.67, range 3-9), were identified and included in the analysis. Method of injury included motor vehicle accident ($n = 29$), motor cycle crash ($n = 220$), blunt head trauma ($n = 212$), fall ($n = 229$), pedestrian hit by car ($n = 216$), and gunshot wound to the head ($n = 27$). Ethnicity was primarily Caucasian ($n = 260$), as well as Hispanic ($n = 227$) and African American ($n = 223$); four patients had unknown ethnicity. Patients received either TTM (43) or standard therapy (71). Within the TTM group eight patients were treated with normothermia after TBI and 35 patients were treated with hypothermia. A logistic regression predicting in hospital mortality with age, GCS, and TM demonstrated that GCS (Beta = 0.572, $P < 0.01$) and age (Beta = -0.029) but not temperature modulation (Beta = 0.797, ns) were significant predictors of in-hospital mortality [$\chi^2(3) = 22.27, P < 0.01$]. A multiple regression predicting number of complications demonstrated that receiving TTM was the main contributor and was associated with a higher number of pulmonary complications ($t = -3.425, P = 0.001$).

CONCLUSION: Exposure to TTM is associated with an increase in pulmonary complications. These findings support more attention to these complications in studies of TTM in TBI patients.

Key words: Hypothermia; Fever; Pneumonia; Traumatic brain injury; Head injury

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Therapeutic hypothermia and normothermia (fever control) are used in patients with traumatic brain injury. This is most commonly done for intracranial hypertension control. The potential complications associated with this therapy when it is used outside of the scope of a closely regulated clinical trial are not well known. This is a retrospective review of patients with traumatic brain injury treated with therapeutic temperature modulation carried out to quantify the non neurological complications associated with this therapy.

O'Phelan KH, Merenda A, Denny KG, Zaila KE, Gonzalez C. Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury. *World J Crit Care Med* 2015; 4(4): 296-301 Available from: URL: <http://www.wjcn.net.com/2220-3141/full/v4/i4/296>.

INTRODUCTION

The systemic cooling of patients with severe traumatic brain injury (TBI) has become an established second tier treatment modality for refractory intracranial hypertension (ICP)^[1-5].

Basic science evidence, anecdotal clinical reports and several low quality trials have suggested that the prophylactic application of this strategy (*i.e.*, primary therapeutic hypothermia) may also exert neuroprotective effects in severe TBI^[6]; however, these benefits have not been confirmed by high-quality human randomized controlled studies. Thus, outside of well-designed clinical trials, the implementation of therapeutic hypothermia after head injury remains justified for and largely limited to patients with uncontrolled ICP elevation. Yet, there are concerns that induced hypothermia may be associated with hemodynamic, pulmonary and infectious complications, as significant pathophysiological changes are known to occur with its induction and maintenance, especially when prolonged for more than 48 h^[7]. However, overall rates of serious hypothermia-related adverse events remain poorly studied in TBI^[8]. Given the knowledge that systemic, non-neurological complications are an independent contributor to morbidity and mortality after TBI^[9], a more rigorous evaluation of the potential adverse effects associated with the use of hypothermia becomes of crucial importance to better determine the safety profile of this strategy in the setting of TBI. The purpose of this study is to examine types and rates of clinical complications in our severe TBI population who are treated with therapeutic temperature modulation (TTM).

MATERIALS AND METHODS

The protocol was reviewed and approved by the institutional review board of our institution. This is a retrospective, observational cohort study. We carefully reviewed the charts for 114 patients with severe TBI admitted to our trauma center between 2007 and 2009. Inclusion criteria included a post resuscitation Glasgow Coma Scale (GCS) < 9, admission to the intensive care unit (ICU) > 24 h and non-penetrating TBI. Patients were divided into two cohorts: The treatment group that received TTM and the control group, which did not. Patients in the temperature modulation group received continuous surface cooling and temperature measurement *via* an indwelling bladder probe. This group included both therapeutic hypothermia with a target temperature of < 36 °C or induced normothermia with a target temperature of 36 °C-37 °C. The control group received intermittent acetaminophen as need to treat fever. The decision to use TTM and the degree of cooling were determined on an individual basis by the

Table 1 Baseline characteristics

	Temperature modulation	Control
No. of patients	44	70
M:F	1:4.5	1:4.4
Mean GCS (SD)	4.6 (1.9)	4.7 (1.9)
Mean age (SD)	33.3 (14.2)	46.5 (20.2)
Mortality	15.9%	31.4%

GCS: Glasgow Coma Scale.

clinical team. The clinical record was reviewed to identify the following events: pneumonia, pneumothorax, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), acute renal failure, cardiac arrhythmias, pulmonary embolism (PE) and deep venous thrombosis (DVT). Pneumonia was identified using a combination of the following criteria: purulent sputum, chest imaging with an infiltrate or consolidation, fever $> 38^{\circ}\text{C}$, leukocytosis ($> 12000 \text{ wbc/mm}^3$ or leukopenia $< 4000 \text{ wbc/mm}^3$) or worsening oxygenation. Pneumothorax and DVT and PE were identified based on imaging and ARDS and ALI were identified using a combination of imaging and arterial blood gas findings. Data on length of stay in the intensive care unit, duration of mechanical ventilation and in hospital mortality were also collected.

Statistical analysis

All data were analyzed using IBM SPSS version 21. A logistic regression was conducted to predict hospital mortality and a multiple regression was used to assess number of complications. Independent variables for both models were age, GCS on admission, and temperature modulation.

RESULTS

Baseline characteristics

One hundred and fourteen patients with severe TBI (mean age = 41.4, SD = 19.1, 93 males), admitted to the Jackson Memorial Hospital Neuroscience ICU (mean GCS = 4.67, range 3-9), were identified and included in the analysis. Method of injury included motor vehicle accident ($n = 29$), motor cycle crash ($n = 20$), blunt head trauma ($n = 12$), fall ($n = 29$), pedestrian hit by car ($n = 16$), and gunshot wound to the head ($n = 7$). Ethnicity was primarily Caucasian ($n = 60$), as well as Hispanic ($n = 27$) and African American ($n = 23$); four patients had unknown ethnicity. Patients received either temperature modulation (*i.e.*, aggressive temperature control, as detailed below) or no continuous modulation (*i.e.*, permissive temperature management), and were monitored for number and type of complications, as well as in hospital mortality.

Temperature modulation

Forty-three patients underwent temperature modulation (TM). Specifically, eight patients were treated with induced normothermia (mean temp = 36.25°C , SD =

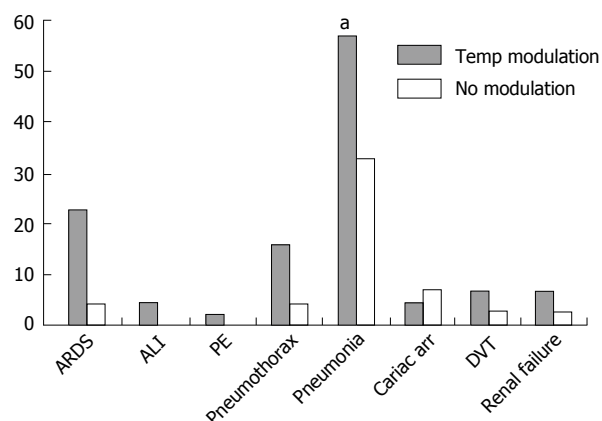


Figure 1 Complications by group. ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; PE: Pulmonary embolism; DVT: Deep venous thrombosis. ^a $P < 0.05$.

0.85) and 35 with mild therapeutic hypothermia (mean temp 34.8°C , SD = 0.75). Temperature modulation was achieved by application of antipyretic agents (acetaminophen) and surface cooling techniques.

Temperature modulation was combined for the remaining analyses (Table 1). In-hospital mortality and number of complications did not statistically differ between normothermia and hypothermia groups [pearson χ^2 (4) = 4.99, ns].

Association of in hospital mortality with temperature modulation

Initially, an unadjusted analysis of mortality suggested a lower rate of mortality in TTM group (6% vs 19%, $P = 0.06$). However, the mean age in the TTM group was younger (33 years, SD 14) vs 46 years (SD 20). As expected, a logistic regression predicting in hospital mortality with age, GCS on admission, and temperature modulation demonstrated that GCS (Beta = 0.572, $P < 0.01$) and age (Beta = -0.029) but not temperature modulation (Beta = 0.797, ns) were significant predictors of in-hospital mortality [χ^2 (3) = 22.27, $P < 0.01$ when mortality was adjusted for age the difference between the groups was not significant].

Association of clinical complications with temperature modulation

A multiple regression predicting number of complications with age, GCS on admission, and temperature modulation demonstrated that receiving temperature modulation was the main contributor and was associated with a higher number of complications [F(3) = 4.59, $P < 0.005$, $t = -3.425$, $P = 0.001$]. Age ($t = 0.71$, ns) and admission GCS ($t = 1.42$, ns) were not significant contributors. Temperature modulation was significantly associated with ARDS, pneumothorax, and pneumonia (Figure 1).

DISCUSSION

The present study examined rates of medical com-

plications associated with the application of TM in patients with severe TBI. However, it was not designed to assess potential clinical benefits of TM as we did not measure long-term functional outcome.

Many physiological effects of hypothermia make its use theoretically attractive in the TBI setting. These include: (1) attenuation of neuro-excitotoxicity, *via* suppression of glutamate release, and ensuing stabilization of the intracellular influx of calcium (effects that ultimately reduce the magnitude of mitochondrial damage and cell demise secondary to the post-injury activation of multiple intracellular enzymatic cascades); (2) stabilization of the blood-brain barrier and blunting of the neuroinflammatory response from microglia, which may limit the development of cerebral edema and oxidative stress^[10-12]; and (3) reduction in the cerebral metabolic rate of oxygen consumption (CMRO₂) by approximately 7% for each degree Celsius decline in body temperature; the latter effect has the dual benefit of preserving brain oxygen stores (thereby conferring protection against cerebral hypoperfusion) and promoting cerebral vasoconstriction with ensuing decrease in ICP^[13,14]. Nevertheless, despite these potential beneficial properties multiple randomized, controlled trials have failed to provide data in support of the primary application of induced hypothermia as a neuroprotective strategy aimed at improving mortality and functional outcome in TBI patients. In addition, concerns have been voiced about possible detrimental effects in trauma patients, with some evidence suggesting an increased risk for hemodynamic and pulmonary complications^[7,15-17]. While data from a recent randomized controlled trial of 48-h hypothermia in TBI patients revealed "no significant differences in the percentage of patients with any individual complication or group of complications, whether critical or non-critical, between groups"^[18], other clinical studies (mostly in patients with stroke and TBI) have reported a higher risk of adverse events, such as pneumonia, when cooling was carried out over longer periods of time (> 48-72 h)^[19,20]. Nevertheless, the inadequate control for possible confounding influences (*e.g.*, poor glycemic control, barbiturate use) in those studies has left uncertainty over a causative link between induced hypothermia and risk of pneumonia or other complications.

The results of our study show that temperature modulation, applied for > 48 h, in the form of normothermia or hypothermia, is not a predictor of in-hospital mortality, but is associated with a significantly increased risk for pulmonary complications (pneumonia, ARDS, and pneumothorax). We were unable to detect a difference between the patients treated with normothermia vs those treated with hypothermia because the sample size was quite small. With regard to pneumothorax, we speculate that the increased incidence of pneumothorax may reflect a more prolonged and aggressive course of mechanical ventilation, with use of higher positive end expiratory pressure levels, in patient developing

severe hypoxemia secondary to pneumonia or ARDS. Thus, the major systemic complications associated with the implementation of temperature modulation in TBI patients appear to be pneumonia and ARDS.

Our finding of an increased incidence of pneumonia with temperature modulation in a purely clinical setting is consistent with the results of 5 published systematic reviews and meta-analyses of randomized controlled clinical trials on the effectiveness of hypothermia in TBI^[8,17,21-23], which identified 6 trials reporting a significant higher rate of pneumonia with induced hypothermia. Similarly, a more recent meta-analysis, which included 23 randomized controlled trials involving adult patients treated with therapeutic hypothermia of various duration (from several hours to several days) and for different indications (including TBI), revealed that patients undergoing systemic cooling were more likely to develop pneumonia (risk ratios, 1.44) compared to control groups^[15].

An increased susceptibility to pneumonia may result from impaired central immune suppression after acute neurological injuries, including TBI. It is also possible that TM may promote the emergence of clinically apparent pneumonia by counteracting the ability of the body to fight infection. A substantial body of evidence from animal studies supports the concept that fever plays a central role in the host response to infection. The immunological effects of temperature elevation within a physiologic febrile range are multiple and beneficial. They include stimulation of neutrophil cell motility and phagocytosis, enhanced expression of receptors involved in mediating antibody responses, promotion of lymphocyte migration to sites of infection, and reduced growth of intracellular bacteria^[24]. While these potentially beneficial consequences of fever cannot be disregarded, they come at the cost of a substantial increase in cerebral metabolic rate of oxygen consumption (CMRO₂), neuroinflammation, activation of calcium-mediated intracellular enzymatic cascades, all of which may promote and exacerbate secondary brain injury. Thus, in TBI patients, a balance must be struck between the benefits of suppressing the above processes with temperature modulation and the potential detrimental effects on host defence mechanisms leading to an increased risk for infection.

It has been suggested that a longer duration of cooling increases risk of infection. This is consistent with the observation, in some clinical studies (mostly in patients with stroke and TBI), of a higher risk of pneumonia when cooling was carried out over more than 48 h duration^[19,20]. This might explain why Clifton's second randomized trial, which limited the use of hypothermia to 48h, did not detect any significant difference in the rates of non-neurological organ dysfunction between hypothermic and normothermic patients. Unfortunately, this adds a layer of complexity to the management of TBI because a period longer than 48 h may be needed to sufficiently control brain edema. This longer

duration may expose the patient to an increased risk of complications. This may offset the potential benefits of prolonged cooling. Severe respiratory failure as a result of ARDS and/or pneumonia may adversely affect cerebral oxygenation and brain energy metabolism, and contribute to secondary brain injury. It is unknown if regional methods of cooling using new devices such as intranasal cooling^[25,26] will offer the neurological benefits of TTM with fewer systemic side effects.

Our findings demonstrate that TM is associated with an increased incidence of pulmonary complications which may restrict the neuroprotective potential of this strategy. Inclusion of protocols to prevent pneumonia in patients with TBI undergoing TM may improve the efficacy of this strategy and should be included in future study protocols.

Our study has several limitations including the retrospective design, a small sample size and no functional measure of neurologic outcome. The questions raised here will need to be demonstrated in a larger study with a prospective design.

In conclusion, our study demonstrates that in patients with TBI, exposure to temperature modulation is associated with a significant increase in pulmonary complications, specifically, pneumonia, ARDS and pneumothorax. These findings support more detailed collection of information about these complications in studies of therapeutic temperature modulation in TBI patients to determine their relevance to outcome. Prospective studies are needed to determine possible detrimental effects on functional neurological recovery that could result from hypothermia-related complications such as ARDS and pneumonia.

COMMENTS

Background

The benefit of hypothermia used for neuroprotection is still debated. The benefits of this therapy have not been proven in large prospective randomized trials for patients with traumatic brain injury. However, the therapy is effective for lowering intracranial pressure. Therefore it is sometimes used for this population. Therefore it is important to understand the potential complications associated with its use.

Research frontiers

Current research efforts focus on the potential benefits of local or regional therapies for temperature management. These studies include trans nasal evaporative cooling which has been studied in cardiac arrest and stroke patients.

Innovations and breakthroughs

This study provides data taken from patients being treated outside of clinical trials. It may be more generalizable than data from carefully controlled trials with a very specific patient population.

Applications

This study should provide support for future studies to more carefully consider and collect data on pulmonary complications in patient being treated with therapeutic temperature modulation. Additionally, these data may inform the cost benefit analysis in a larger prospective study utilizing temperature management in this population.

Terminology

Therapeutic hypothermia or targeted temperature management: Is a therapy that tries to achieve and maintain a specific body temperature to mitigate tissue injury and improve outcome.

Peer-review

This retrospective review has issues with lack of definitions of the key outcome measures used.

REFERENCES

- 1 **Bloch M.** Cerebral effects of rewarming following prolonged hypothermia: significance for the management of severe cranio-cerebral injury and acute pyrexia. *Brain* 1967; **90**: 769-784 [PMID: 6075810]
- 2 **Clifton GL,** Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC. A phase II study of moderate hypothermia in severe brain injury. *J Neurotrauma* 1993; **10**: 263-271; discussion 273 [PMID: 8258839]
- 3 **Marion DW,** Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg* 1993; **79**: 354-362 [PMID: 8360731]
- 4 **Shiozaki T,** Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg* 1993; **79**: 363-368 [PMID: 8360732]
- 5 **Shapiro HM,** Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *J Neurosurg* 1974; **40**: 90-100 [PMID: 4808489]
- 6 **Pomeranz S,** Safar P, Radovsky A, Tisherman SA, Alexander H, Stezoski W. The effect of resuscitative moderate hypothermia following epidural brain compression on cerebral damage in a canine outcome model. *J Neurosurg* 1993; **79**: 241-251 [PMID: 8331408]
- 7 **Polderman KH.** Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality--Part 2: Practical aspects and side effects. *Intensive Care Med* 2004; **30**: 757-769 [PMID: 14767590]
- 8 **Peterson K,** Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *J Neurotrauma* 2008; **25**: 62-71 [PMID: 18355159]
- 9 **Lim HB,** Smith M. Systemic complications after head injury: a clinical review. *Anaesthesia* 2007; **62**: 474-482 [PMID: 17448059]
- 10 **Schmitt KR,** Diestel A, Lehnardt S, Schwartlander R, Lange PE, Berger F, Ullrich O, Abdul-Khaliq H. Hypothermia suppresses inflammation via ERK signaling pathway in stimulated microglial cells. *J Neuroimmunol* 2007; **189**: 7-16 [PMID: 17651818]
- 11 **Gibbons H,** Sato TA, Dragnow M. Hypothermia suppresses inducible nitric oxide synthase and stimulates cyclooxygenase-2 in lipopolysaccharide stimulated BV-2 cells. *Brain Res Mol Brain Res* 2003; **110**: 63-75 [PMID: 12573534]
- 12 **Dempsey RJ,** Combs DJ, Maley ME, Cowen DE, Roy MW, Donaldson DL. Moderate hypothermia reduces postischemic edema development and leukotriene production. *Neurosurgery* 1987; **21**: 177-181 [PMID: 2821445]
- 13 **Keresztes PA,** Brick K. Therapeutic hypothermia after cardiac arrest. *Dimens Crit Care Nurs* 2006; **25**: 71-76 [PMID: 16552276]
- 14 **Steen PA,** Newberg L, Milde JH, Michenfelder JD. Hypothermia and barbiturates: individual and combined effects on canine cerebral oxygen consumption. *Anesthesiology* 1983; **58**: 527-532 [PMID: 6859582]
- 15 **Geurts M,** Macleod MR, Kollmar R, Kremer PH, van der Worp HB. Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis. *Crit Care Med* 2014; **42**: 231-242 [PMID: 23989182]
- 16 **Clifton GL,** Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, Muizelaar JP, Wagner FC, Marion DW, Luerksen TG, Chesnut RM, Schwartz M. Lack of effect of induction of hypothermia after acute

- brain injury. *N Engl J Med* 2001; **344**: 556-563 [PMID: 11207351]
- 17 **Alderson P**, Gadkary C, Signorini DF. Therapeutic hypothermia for head injury. *Cochrane Database Syst Rev* 2004; (4): CD001048 [PMID: 15495003]
 - 18 **Clifton GL**, Drever P, Valadka A, Zygun D, Okonkwo D. Multicenter trial of early hypothermia in severe brain injury. *J Neurotrauma* 2009; **26**: 393-397 [PMID: 19245306]
 - 19 **Shiozaki T**, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, Fujimi S, Nakamori Y, Tanaka H, Shimazu T, Sugimoto H. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg* 2001; **94**: 50-54 [PMID: 11147897]
 - 20 **Schwab S**, Georgiadis D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 2001; **32**: 2033-2035 [PMID: 11546893]
 - 21 **Henderson WR**, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ. Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis. *Intensive Care Med* 2003; **29**: 1637-1644 [PMID: 12915937]
 - 22 **Sydenham E**, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Syst Rev* 2009; (2): CD001048 [PMID: 19370561]
 - 23 **Georgiou AP**, Manara AR. Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review. *Br J Anaesth* 2013; **110**: 357-367 [PMID: 23353036]
 - 24 **Young P**, Saxena M, Eastwood GM, Bellomo R, Beasley R. Fever and fever management among intensive care patients with known or suspected infection: a multicentre prospective cohort study. *Crit Care Resusc* 2011; **13**: 97-102 [PMID: 21627577]
 - 25 **Abou-Chebl A**, Sung G, Barbut D, Torbey M. Local brain temperature reduction through intranasal cooling with the RhinoChill device: preliminary safety data in brain-injured patients. *Stroke* 2011; **42**: 2164-2169 [PMID: 21680904]
 - 26 **Castrén M**, Nordberg P, Svensson L, Taccone F, Vincent JL, Desruelles D, Eichwede F, Mols P, Schwab T, Vergnion M, Storm C, Pesenti A, Pacht J, Guérisset F, Elste T, Roessler M, Fritz H, Durnez P, Busch HJ, Inderbitzen B, Barbut D. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation* 2010; **122**: 729-736 [PMID: 20679548]

P- Reviewer: Inchauspe A, Ntoumenopoulos G **S- Editor:** Ji FF

L- Editor: A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

