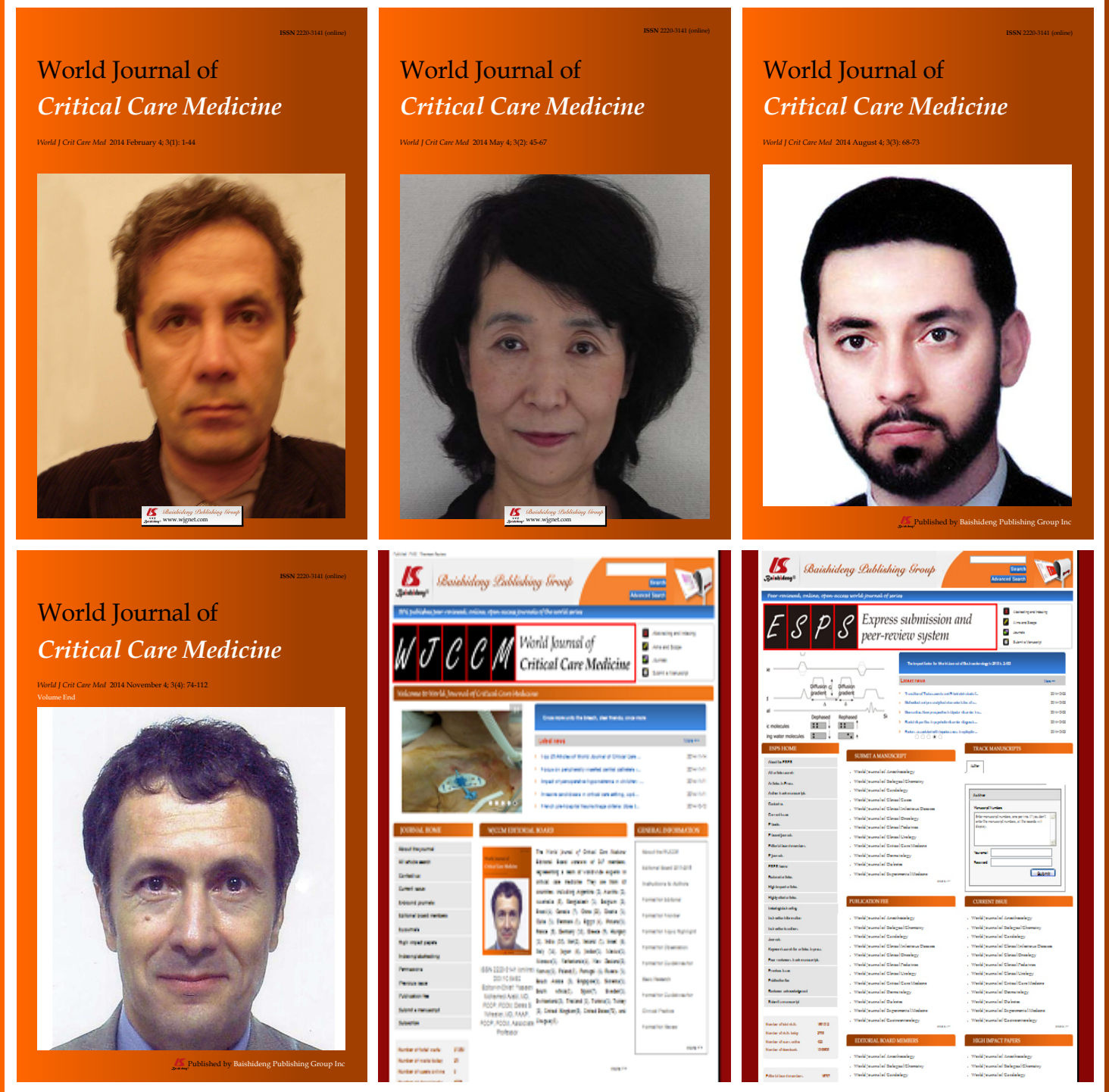
ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

2014 Bound Volume 3 Issue 1-4: 1-112



Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

A peer-reviewed, online, open-access journal of critical care medicine

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).

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2014 February 4; 3(1): 1-44

Baishideng Publishing Group
www.wjgnet.com

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 3 Number 1 February 4, 2014

World Journal of Critical Care Medicine
Volume 3 Number 1 February 4, 2014

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

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: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-6555-7188
Telephone: +852-3177-9906

E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
February 4, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3141/g_info_20100722180909.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.1

World J Crit Care Med 2014 February 4; 3(1): 1-7
ISSN 2220-3141 (online)

EDITORIAL

Rhabdomyolysis, compartment syndrome and thermal injury

Yusuf Kenan Coban

Yusuf Kenan Coban, Burn Unit and Department of Plastic Surgery, Inonu University Turgut Ozal Medical Centre, 44280 Malatya, Turkey
Author contributions: Coban YK solely contributed to this paper.
Correspondence to: Yusuf Kenan Coban, Professor, Burn Unit and Department of Plastic Surgery, Inonu University Turgut Ozal Medical Centre, 44280 Malatya, Turkey. ykenanc@yahoo.com
Telephone: +90-422-2374780 Fax: +90-422-2374780
Received: May 7, 2013 Revised: September 4, 2013
Accepted: October 16, 2013
Published online: February 4, 2014

Abstract

Rhabdomyolysis (RML) after electrical burns and crush injuries is a well-known clinical entity, but its occurrence following thermal injury has not gained so much attention. Capillary leak syndrome and following polycompartmental syndrome are devastating end results of major thermal injuries. In the current review, polycompartment syndrome within the clinical picture of systemic oedema and its relationship to RML is discussed along with its management and prevention.

Key words: Capillary leak syndrome; Rhabdomyolysis; Thermal injury

Core tip: In the current review, polycompartment syndrome within the clinical picture of systemic oedema and its relationship to rhabdomyolysis is discussed along with its management and prevention.

Coban YK. Rhabdomyolysis, compartment syndrome and thermal injury. *World J Crit Care Med* 2014; 3(1): 1-7 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/1.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.1

DEFINITION

Rhabdomyolysis (RML) is defined as muscle damage with dissolution of the skeletal muscle fibre and results in release of potentially toxic intracellular components into the systemic circulation. A classical triad of symptoms includes muscle pain, prostration and dark pigmented urine. Urine pigmentation only manifests itself when the renal threshold for myoglobulin (MB) is exceeded. In 1940-1941, RML syndrome was first described in patients with crush injury secondary to building destruction during wartime[1]. In later decades, it was understood that RML is not confined to crush injuries, but is also associated with thermal injuries and other medical causes. Although direct muscle injury remains the most common cause of RML, additional causes include toxins, endocrinopathies, malignant hyperthermia, neuroleptic malignant syndrome, electrolyte alterations, diabetic ketoacidosis, non-ketotic hyperosmolar coma, severe hypo- or hyperthyroidism and bacterial or viral infections. Generally speaking, RMLs can be divided into two categories as shown in Figure 1.

PATHOPHYSIOLOGY

The scenario is seen after severe crush and thermal or electric injuries in addition to direct muscle injury. In other words, there may be a combination of both direct muscle injury and compartment syndrome in the same clinical picture. On the other hand, the primary mechanism for position-related RML is reperfusion of damaged tissue after a period of ischaemia and the release of necrotic muscle material into the circulation after pressure is relieved. In severe burns, capillary leak syndrome leading to polycompartmental syndrome is also responsible for the development of RML *via* several mecha-

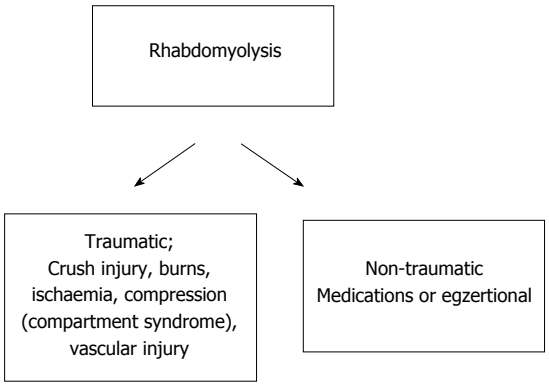


Figure 1 General classification of rhabdomyolysis.

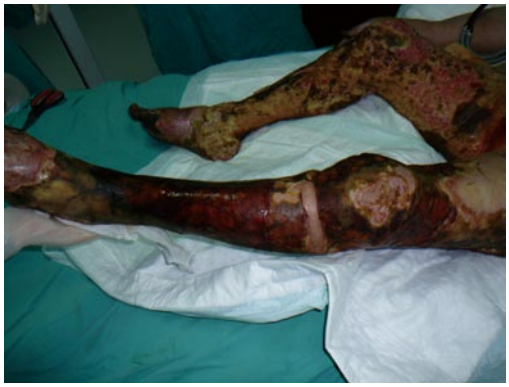


Figure 2 An example for full-thickness burns of both lower extremities.

nisms including loss of vasomotor tone of arterioles, collapse of thinner-walled veins, and the overall loss of the pressure gradient between the arterial and venous system. As the blood flow decreases, the tissues become progressively more ischaemic, thereby leading to further necrosis and oedema.

Muscle necrosis is triggered by derangements in oxidative or glycolytic energy production with resulting ATP depletion. In the presence of concomitant ATP depletion, free Ca^{2+} content in the myocyte increases due to failure of Ca^{2+} efflux mediated by the ATPase-driven Ca^{2+} pump. Influx from the extracellular compartment into muscle cells includes water, Na^{+}, Cl^{-} and Ca^{2+}. Muscle cells swell due to the accumulation of intracellular solutes and a reduction in active ion extrusion. Within minutes of trauma, intramuscular pressure may exceed arterial blood pressure within the intracompartmental space. Hypovolaemia develops, followed by haemodynamic shock, hypocalcaemia, and hyponatraemia in the context of trauma and burns. Progressive hypovolaemia is thought to contribute to the formation of casts that obstruct renal tubules and to renal vasoconstriction involving afferent glomerular arterioles and glomerular capillaries[2].

As the skeletal muscle (SM) is a principal actor that plays a major role in the pathophysiology of RML, its distribution within the body is worthy of mention. Subcutaneous muscle accounts for approximately 40% of total body mass for adult males and 29% for adult females. Depending on gender, age and health status, one-third and one-half of body protein resides within SM[3]. There is growing awareness of the importance of SM in many physiological and disease processes[4]. Janssen *et al*[5] studied skeletal muscle mass measurement in whole body distribution by magnetic resonance imaging. They found that the lower body had more SM mass than upper body regions in both sexes. As the lower extremity bears much of SM mass of total body SM mass, full-thickness burns of the lower extremity pose a higher risk for development of fatal RML (Figure 2). One might speculate that immobilization is more commonly seen after lower extremity full-thickness burns when compared to the upper body parts, and this may mean increased risk of RML for lower extremity burns.

LABRATORY DIAGNOSIS AND MORTALITY

The diagnosis of RML is based on the measurement of creatinine kinase (CK) in serum or plasma. Plasma and urine myoglobin CK measurement might be useful in the early stage of the syndrome[6]. Patient monitoring is pivotal (the mortality rate is as high as 8%) and should be aimed at preventing the detrimental consequences. Mortality for patients with RML secondary to flame burns seems to be high[7]. Stewart *et al*[8] studied percentage of full-thickness burns, percentage of total body surface area (TBSA) burned, injury severity score, peak CK and acute kidney injury (AKI) in burn patients. They found that the log peak CK correlated with stage of AKI[8]. Another study revealed that 28% of severely burned patients developed AKI during acute resuscitation[9]. In a retrospective study of 714 patients, eight were reported to have RML and these cases had poor survival[10].

THERMAL INJURY AND RHABDOMYOLYSIS

Several issues related to the subject are present. These are the role of albumin and fluid therapy, capillary leak syndrome and comorbid situations.

Albumin in severe burns

Lower albumin concentrations are commonly observed in older persons and are associated with worse health outcomes and mortality[11]. Albumin is a negative acute-phase protein that decreases with ongoing inflammation, and many of the reported associations with albumin may reflect this[12]. Serum albumin concentration $\leqslant$ 30 g/L was reported to be associated with a twofold increase in organ dysfunction[13]. The optimal resuscitation algorithm including albumin supplementation remains elusive for patients with large burn injuries. Park *et al*[14] compared the use of 5% albumin in the first 24 h with other protocols not using albumin solution. They found

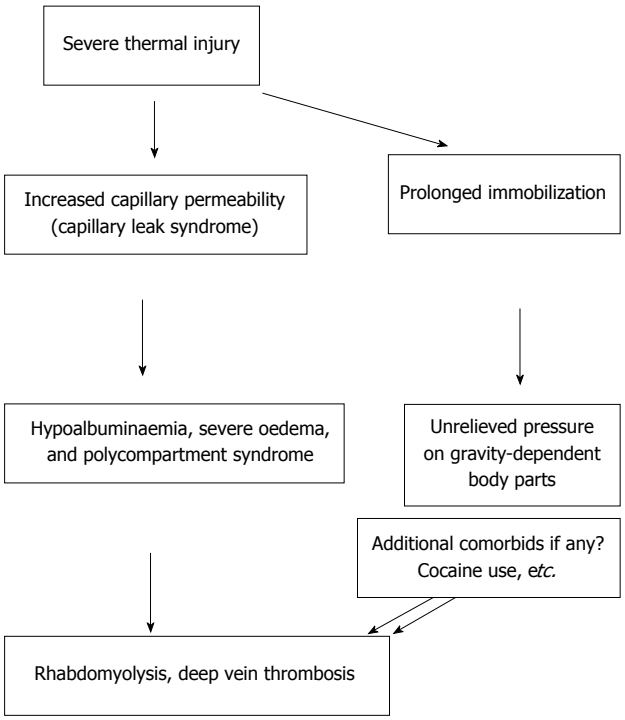


Figure 3 Pathogenic mechanisms for development of rhabdomyolysis in severe thermal injury.

that their new protocol decreased ventilator days and mortality, whereas another study revealed an opposite outcome. Currently, there is no consensus on using albumin replacement therapy for acute burn resuscitation[15]. The albumin molecule, being smaller (69 kDa) than the globulin molecule (90-156 kDa), will leak at a relatively earlier stage of the disease (with a moderate increase in capillary pore size) than globulin. This leads to albumin/globulin reversal. In cases with severe permeability changes related with rapid progression to larger pore size with simultaneous leak of both albumin and globulin, albumin/globulin reversal will not occur. Kumar's[16] study showed that patients with albumin protein values less than 5.0 g/dL showed higher mortality (95%) compared to those in other groups with more than 5.0 g/dL.

Capillary leak syndrome

Major burns are characterised by an initial capillary leak that requires fluid resuscitation for haemodynamic stabilization. The extensive capillary damage that follows thermal injury is responsible for massive plasma extravasation into burned tissues, with consequent hypovolaemia, abdominal hypertension and extremity compartmental syndrome necessitating fasciotomy, prolonged mechanical ventilation and hospital stay. Increased compartmental pressure poses a risk for RML. In local compartmental syndrome, the pathology is restricted to a unique body region and does not cause a life-threatening systemic condition. However, capillary leak syndrome, whether the cause is idiopathic or due to severe burns, causes hypovolaemic shock due to marked plasma shifts from the intravascular to the extravascular space. This presents as the characteristic triad of hypotension, haemoconcentration and hypoalbuminaemia. The reason is due to leakage of fluids and macromolecules (up to 900 kDa) into tissues. Systemic capillary leak syndrome is a transient event, and less than 150 cases have been reported. Systemic oedema causes multiple compartment syndrome, which needs emergency fasciotomies[17]. Hypoalbuminaemia always associates with the picture of systemic oedema and polycompartmental syndrome.

Direct damage to the striated muscle by high electrical voltage is well understood[18]. In thermal burns without direct muscle injury, the actual trigger for RML often remains unexplained. The majority of the publications on the subject are single case reports[19,20]. Prolonged immobilization following unconsciousness and repeated surgical procedures has been suggested to trigger RML in thermally injured patients. However, there may be several factors contributing to the development of RML in the context of severe thermal burns (Figure 3).

Ideal formulation of fluid therapy in burn shock

Less than 20% of burn injuries are associated with minimal fluid shifts and can generally be resuscitated with oral hydration. Current recommendations are to initiate formal intravascular fluid resuscitation when the surface area burned is greater than 20%. The ideal burn resuscitation is the one that effectively restores plasma volume, with no adverse effects. Isotonic crystalloids, hypertonic solutions and colloids have been used for this purpose, but every solution has its advantages and disadvantages. None of them is ideal, and none is superior to any of the others. Too vigorous resuscitative efforts may lead to severe protein depletion and further oedema accumulation into both burned and unburned tissues.

A condition of fluid unresponsiveness is present throughout the first 12 h of the post-burn period. The administration of supranormal volumes fails in the first 24 h to achieve normal preload volumes. The fluid creep started in the 1990s with an increasing proportion of the first 24 hours' fluid delivery above the 4 mL/kg TBSA% (Parkland formula). The first alerts were published under the form of case reports of increased mortality due to abdominal compartment syndrome and respiratory failure. While under-resuscitation was the major cause of mortality among burned patients until the 1980s, over-resuscitation has become an important source of complications[21]. Several studies have supported that patients who receive larger volumes of resuscitation fluid are at higher risk of injury complications such as pneumonia and extremity compartment syndrome. Hypertonic saline should be reserved for providers experienced in this approach. Plasma sodium concentrations should be closely monitored to avoid excessive hypernatraemia. Administration of high-dose ascorbic acid may decrease the overall fluid requirements, and is worthy of further study[22].

Resuscitation fluids influence the inflammatory response to burns in different ways and it may be possible

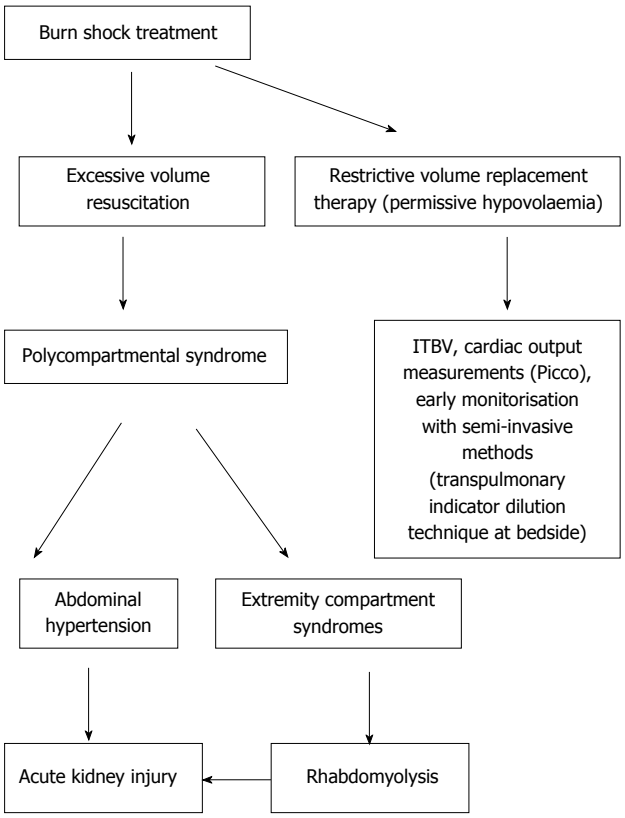


Figure 4 Possible scenarios during burn shock resuscitation. ITBV: Intrathoracic blood volume.

Table 1 Therapeutic goals of fluid resuscitation and therapeutic measures in thermal injury

Goal	Measure
Preventing hypovolaemia and shock	Fluid overloading (with rationing prehospital fluid delivery)
Improving organ perfusion	Mannitol, high dose vitamin C administration (avoiding early colloids)
Reducing capillary leak and oedema	Not known
Reducing inflammatory storm	Haemodialysis, plasmapheresis, *etc.*
Avoiding polycompartment syndrome	Permissive hypovolaemia

therefore to affect this response using appropriate fluid at the appropriate time[23]. Table 1 shows the goals of early fluid resuscitation in major burns.

Starches are effective volume expanders and early use of newer formulations may limit resuscitation requirements and burn oedema[24]. It has been shown that post-burn oedema is detrimental to organ function and that the deleterious effect is proportional to the amount of extravasated fluids[25]. Arlati *et al*[26] compared permissive hypovolaemia administered by a hemodynamic-oriented approach with Parkland formula resuscitation throughout the first 24 h period. They found permissive hypovolaemia allowed for less volume infusion, a reduced positive fluid balance and significantly lesser multiple organ dysfunction syndrome (MODS) score values than the Parkland formula.

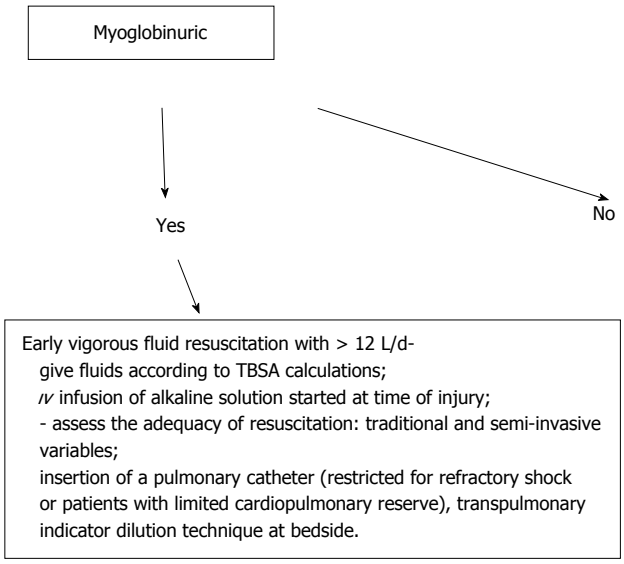


Figure 5 Algorithm for established clinical picture of rhabdomyolysis in burn victims. TBSA: Total body surface area.

Permissive hypovolaemia seems safe and well tolerated by burn patients. It seems effective in reducing multiple organ dysfunction due to induced oedema fluid accumulation and inadequate O_2 tissue utilization. It has been speculated that the insensitivity of cardiac preload to increase by even the most aggressive regimen might derive from the combination of both increased capillary permeability and higher hydrostatic pressure than most forms of hypovolaemic shock. A supranormal resuscitation volume might exacerbate post-burn oedema accumulation by unnecessarily increasing both the amount and length of fluid extravasation. The reduction of volume given was obtained throughout the period of maximum capillary damage. This would be impossible without the use of invasive haemodynamic monitoring as both intrathoracic blood volume (ITBV, as a cardiac preload indicator) and cardiac output measurements generated[26]. The PICCO system allows both ITBV and cardiac output measurements. ITBV and cardiac output measurement are earlier and more sensitive indicators of critical hypovolaemia than vital signs, hourly urine output and central venous pressure. A haemodynamic-oriented approach to burn shock resuscitation is gaining more acceptance for direct cardiac preload estimation nowadays (Figure 4).

Compartment syndrome

Burns and toxic causes may lead to polycompartment syndrome during fluid resuscitation if given at too high a dose. Compartment syndrome can be classified as primary (pathology within the compartment) and secondary (no primary pathology or injury within the compartment)[27]. SM compartments are especially susceptible to this type of injury. Thermal injuries, in particular full-thickness burns, cause secondary tissue constriction eschars and oedema. Fluid shifts associated with major burns adding to extravolume pressure may contribute to

Table 2 Risk factors for rhabdomyolysis

Risk factors for position-related rhabdomyolysis
Long-lasting surgery (more than 5-6 h) or prolonged immobilization (coma, unconsciousness)
Body weight more than 30% of ideal body weight
Pre-existing azotaemia
Diabetes
Hypertension
Uncontrolled extracellular volume depletion
Associated drug abuse (cocaine, *etc.*)

the development of compartment syndrome. The obtruded patient with prolonged limb compression, either during surgery or postoperative sedation, is at particular risk for development of an extremity compartment syndrome that may go unnoticed. In terms of the role of increasing CK levels and myoglobinuria, these are nonspecific signs of muscle necrosis and late signs of untreated irreversible compartment syndromes.

In most compartments, pressures > 30 mmHg critically compromise organ perfusion. According to the most recognised explanation of the syndrome, A-V gradient pressure theory, the perfusion of the intracompartmental tissues is hindered by the elevation of the interstitial fluid pressure above the level of the capillaries. The capillary pressure on the arterial end and the venous ends are 30 and 10 mmHg, respectively. Excessive volume resuscitation to prevent and treat burn shock may lead to intra-abdominal compartment syndrome, which is probably an underestimated contributor to the development of acute kidney injury after burn shock. The earliest effect of raising the intra-abdominal pressure (IAP) is to reduce visceral perfusion to organs. Subtle interactions with other noxious organ-damaging effects may be indistinguishable in a multifactorial setting. With higher IAP, more overt symptoms may be seen such as hypercarbic and hypoxaemic respiratory failure. Mortality rates of this clinical picture are between 70% and 100%.

Comorbid situations

The only cause of raised CK in thermal burns patients remains the involvement of muscles in deep burns. However, RML may occur in patients with superficial burns who had cocaine abuse[28]. Table 2 shows risk factors for development of RML. If any of these is present in the burn victim, RML may occur without the effect of presence of burn injury. Prolonged immobilization (*e.g.,* anaesthesia, coma, drug- or alcohol-induced unconsciousness) has been reported to induce RML due to unrelieved pressure on gravity-dependent body parts. Lateral decubitus, lithotomy, sitting, knee-to-chest and prone positions are reported to be the most common positions leading to RML. One of the risk factors for position-related RMLs was identified as having a bodyweight more than 30% greater than the ideal body weight .

RHABDOMYOLYSIS-INDUCED RENAL FAILURE

Leakage of intracellular contents such as myoglobulin (MB), CK, K, aldolase phosphate, lactate dehydrogenase, aspartate transaminase and urate into the extracellular space occurs in RML[29]. After complete sarcolemmal destruction, MB is released into the systemic circulation, leading to renal tubular obstruction. The extent of renal damage is dependent on the amount of volume deficit and renal ischaemia. When MB levels reach 100 mg/dL, dark, tea-coloured urine is seen. The principal goal is to prevent renal failure in cases of RML by aggressive fluid replacement and forced diuresis. If acute renal failure cannot be prevented by these measures, renal replacement therapy becomes mandatory. CK and MB levels must be routinely measured in all patients on admission.

In human patients, increased serum and perfusate levels of MB and CK during isolated limb perfusion have been shown for melanoma and sarcoma treatments[30]. Exertional muscle damage produced by eccentric exercise in healthy individuals has been shown to cause profound CK and MB elevations without renal impairment[31,32].

RML-induced renal failure is caused by the precipitation of myoglobin in the renal tubules. Early aggressive resuscitation with either normal saline or ringer lactate to maintain an adequate urine output is the most employed intervention in preventing the development of renal failure[33]. Therapeutic options include the correction of the hypovolaemia with sufficient fluid supply, the prevention of oliguria using loop diuretics, alkalinization of urine, normalization of serum electrolytes and decomposition of compartment syndromes. RML can be complicated by ARF occurring in 4%-33% of the patients[34]. Emerging data overwhelmingly suggest that fluid overload in critically ill patients may be associated with adverse outcomes. Over and under fluid resuscitation may endanger renal function in several ways. So, management of such patients should include a strategy of early resuscitation followed by a careful assessment of fluid status and early initiation of renal replacement therapy[35].

With increased pulmonary intestinal fluid during fluid administration, hypoxia is a frequent sequela in the context of systemic oedema. The septic patient with capillary leak syndrome is then diagnosed as having acute respiratory distress syndrome (ARDS) and placed on mechanical ventilation. Hyroxyethyl starch (HES) has negative effects on coagulation and causes an osmotic nephrosis that can lead to renal impairment. So, HES usage during fluid management of severe burn injuries may increase the risk of acute kidney injury (AKI)[36]. On the other hand, persistent fluid overload in AKI patients may lead to development of ARDS. Abdominal compartment syndrome (ACS) has been described with extensive abdominal fluid and impaired renal function[37]. ACS is associated with resuscitation volumes of 300

mL/kg per 24 h. Figure 5 shows possible negative consequences of over-resuscitation. Burn physicians must evolve their practices to avoid over-resuscitation or they should use more sensitive markers of organ perfusion than urine output.

Figure 5 proposes that myoglobinuric burn patients must be protected from AKI by *iv* infusion of alkaline solution. This regimen stabilizes the circulation and mobilizes oedema fluids sequestered in the injured muscles into the circulation, corrects hyperkalaemia and acidosis and protects against the nephrotoxic effects of myoglobulinuria and uricosuria[38].

Muscle injury as a consequence of burn injury may have led to elevation in serum creatinine concentrations by increased release of creatinine in circulation while glomerular filtration rate is unaffected. On the other hand, serum creatinine may already be increased on admission leading to a false low prevalence of AKI when defined as a relative increase of serum creatinine. Burn injury patients with AKI have a worse prognosis that is almost linearly correlated with severity of AKI. Although AKI with renal replacement therapy remains prevalent in populations with severe burn injury, the outcome improved[26,39].

CONCLUSION

RML is still one of the leading causes of fatality in major burns. Massive destruction of muscular tissue leads to RML, defined as CK elevation combined with organ damage, which requires immediate diagnostic and therapeutic intervention. It appears that RML following extensive full-thickness burns may be more common than previously suggested. So health professionals dealing with burn therapy must pay close attention against possible development of RML. Especially prolonged immobilization and surgeries in certain positions can be preventable, while health professionals are taking measures against these risk factors[40-42]. Judicious fluid resuscitation remains a basic, but potentially life-saving duty of all involved in the care of the severely burned patient. However, it is not known whether serious complications like secondary abdominal hypertension are iatrogenic or truly unavoidable in the most seriously burned patients. Our uncertainty regarding the basic pathophysiology of thermal injury and resuscitation may be the explanation. A number of alternative strategies have been explored in relatively small trials. Further advances may potentially arise from modulation of the inflammatory response through improved therapies and fluid or from new insights into the basic mechanism of cellular injury and its treatment.

REFERENCES

1 **Better OS**, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 1990; **322**: 825-829 [PMID: 2407958 DOI: 10.1056/NEJM199003223221207]

2 **Wiedemann HP**, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767]

3 **Heymsfield SB**, McManus C, Stevens V, Smith J. Muscle mass: reliable indicator of protein-energy malnutrition severity and outcome. *Am J Clin Nutr* 1982; **35**: 1192-1199 [PMID: 6805298]

4 **Gallagher D**, Heymsfield SB. Muscle distribution: variations with body weight, gender, and age. *Appl Radiat Isot* 1998; **49**: 733-734 [PMID: 9569594 DOI: 10.1016/S0969-8043(97)00096-1]

5 **Janssen I**, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol* (1985) 2000; **89**: 81-88 [PMID: 10904038]

6 **Visweswaran P**, Guntupalli J. Rhabdomyolysis. *Crit Care Clin* 1999; **15**: 415-428, ix-x [PMID: 10331135 DOI: 10.1016/S0749-0704(05)70061-0]

7 **Lazarus D**, Hudson DA. Fatal rhabdomyolysis in a flame burn patient. *Burns* 1997; **23**: 446-450 [PMID: 9426917 DOI: 10.1016/S0305-4179(97)89767-7]

8 **Stewart IJ**, Cotant CL, Tilley MA, Huzar TF, Aden JK, Snow BD, Gisler C, Kramer KW, Sherratt JR, Murray CK, Blackbourne LH, Renz EM, Chung KK. Association of rhabdomyolysis with renal outcomes and mortality in burn patients. *J Burn Care Res* 2013; **34**: 318-325 [PMID: 22955163]

9 **Mosier MJ**, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL, Tompkins RG, Herndon DN. Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. *J Burn Care Res* 2010; **31**: 83-92 [PMID: 20061841 DOI: 10.1097/BCR.0b013e3181cb8c87]

10 **Stollwerck PL**, Namdar T, Stang FH, Lange T, Mailänder P, Siemers F. Rhabdomyolysis and acute renal failure in severely burned patients. *Burns* 2011; **37**: 240-248 [PMID: 20965664 DOI: 10.1016/j.burns.2010.09.009]

11 **Naber TH**, de Bree A, Schermer TR, Bakkeren J, Bär B, de Wild G, Katan MB. Specificity of indexes of malnutrition when applied to apparently healthy people: the effect of age. *Am J Clin Nutr* 1997; **65**: 1721-1725 [PMID: 9174466]

12 **Huang Y**, Shinzawa H, Togashi H, Takahashi T, Kuzumaki T, Otsu K, Ishikawa K. Interleukin-6 down-regulates expressions of the aldolase B and albumin genes through a pathway involving the activation of tyrosine kinase. *Arch Biochem Biophys* 1995; **320**: 203-209 [PMID: 7625825 DOI: 10.1016/0003-9861(95)90001-2]

13 **Eljaiek R**, Dubois MJ. Hypoalbuminemia in the first 24h of admission is associated with organ dysfunction in burned patients. *Burns* 2013; **39**: 113-118 [PMID: 22683139]

14 **Park SH**, Hemmila MR, Wahl WL. Early albumin use improves mortality in difficult to resuscitate burn patients. *J Trauma Acute Care Surg* 2012; **73**: 1294-1297 [PMID: 23117385 DOI: 10.1097/TA.0b013e31827019b1]

15 **Melinyshyn A**, Callum J, Jeschke MC, Cartotto R. Albumin supplementation for hypoalbuminemia following burns: unnecessary and costly! *J Burn Care Res* 2013; **34**: 8-17 [PMID: 23128130]

16 **Kumar P**. Grading of severity of the condition in burn patients by serum protein and albumin/globulin studies. *Ann Plast Surg* 2010; **65**: 74-79 [PMID: 20548219 DOI: 10.1097/SAP.0b013e3181c47d71]

17 **Pitt RM**, Parker JC, Jurkovich GJ, Taylor AE, Curreri PW. Analysis of altered capillary pressure and permeability after thermal injury. *J Surg Res* 1987; **42**: 693-702 [PMID: 3586633 DOI: 10.1016/0022-4804(87)90013-8]

18 **Fish RM**. Electric injury, Part II: Specific injuries. *J Emerg Med* 2000; **18**: 27-34 [PMID: 10645833 DOI: 10.1016/S0736-4679(99)00158-4]

19 **Guéchot J**, Cynober L, Lioret N, Bétourné C, Saizy R, Giboudeau J. Rhabdomyolysis and acute renal failure in a patient with thermal injury. *Intensive Care Med* 1986; **12**:

159-160 [PMID: 3734248]
20 **Lee MT**, Lee XL, Hsieh CS. Survival of near fatal rhabdomyolysis following flame burn in a 25-year-old patient. *Burns* 2006; **32**: 634-639 [PMID: 16764995 DOI: 10.1016/j.burns.2005.12.007]
21 **Dulhunty JM**, Boots RJ, Rudd MJ, Muller MJ, Lipman J. Increased fluid resuscitation can lead to adverse outcomes in major-burn injured patients, but low mortality is achievable. *Burns* 2008; **34**: 1090-1097 [PMID: 18468802 DOI: 10.1016/j.burns.2008.01.011]
22 **Baxter CR**. Problems and complications of burn shock resuscitation. *Surg Clin North Am* 1978; **58**: 1313-1322 [PMID: 734611]
23 **Pham TN**, Cancio LC, Gibran NS. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res* 2008; **29**: 257-266 [PMID: 18182930]
24 **Tricklebank S**. Modern trends in fluid therapy for burns. *Burns* 2009; **35**: 757-767 [PMID: 19482429 DOI: 10.1016/j.burns.2008.09.007]
25 **Dries DJ**, Waxman K. Adequate resuscitation of burn patients may not be measured by urine output and vital signs. *Crit Care Med* 1991; **19**: 327-329 [PMID: 1999092 DOI: 10.1097/00003246-199103000-00007]
26 **Arlati S**, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. *Resuscitation* 2007; **72**: 371-378 [PMID: 17137702 DOI: 10.1016/j.resuscitation.2006.07.010]
27 **Sanghavi R**, Aneman A, Parr M, Dunlop L, Champion D. Systemic capillary leak syndrome associated with compartment syndrome and rhabdomyolysis. *Anaesth Intensive Care* 2006; **34**: 388-391 [PMID: 16802499]
28 **Welch RD**, Todd K, Krause GS. Incidence of cocaine-associated rhabdomyolysis. *Ann Emerg Med* 1991; **20**: 154-157 [PMID: 1996798]
29 **Khan FY**. Rhabdomyolysis: a review of the literature. *Neth J Med* 2009; **67**: 272-283 [PMID: 19841484]
30 **Hohenberger P**, Haier J, Schlag PM. Rhabdomyolysis and renal function impairment after isolated limb perfusion--comparison between the effects of perfusion with rhTNF alpha and a 'triple-drug' regimen. *Eur J Cancer* 1997; **33**: 596-601 [PMID: 9274441 DOI: 10.1016/S0959-8049(97)00013-0]
31 **Clarkson PM**, Kearns AK, Rouzier P, Rubin R, Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. *Med Sci Sports Exerc* 2006; **38**: 623-627 [PMID: 16679975 DOI: 10.1249/01.mss.0000210192.49210.fc]
32 **Oh JY**, Laidler M, Fiala SC, Hedberg K. Acute exertional rhabdomyolysis and triceps compartment syndrome during a high school football cAMP. *Sports Health* 2012; **4**: 57-62 [PMID: 23016070]
33 **Shapiro ML**, Baldea A, Luchette FA. Rhabdomyolysis in the intensive care unit. *J Intensive Care Med* 2012; **27**: 335-342 [PMID: 21436168 DOI: 10.1177/0885066611402150]
34 **Bagley WH**, Yang H, Shah KH. Rhabdomyolysis. *Intern Emerg Med* 2007; **2**: 210-218 [PMID: 17909702]
35 **Yerram P**, Karuparthi PR, Misra M. Fluid overload and acute kidney injury. *Hemodial Int* 2010; **14**: 348-354 [PMID: 20955269 DOI: 10.1111/j.1542-4758.2010.00498.x]
36 **Vlachou E**, Gosling P, Moiemen NS. Hydroxyethylstarch supplementation in burn resuscitation--a prospective randomised controlled trial. *Burns* 2010; **36**: 984-991 [PMID: 20558004 DOI: 10.1016/j.burns.2010.04.001]
37 **Shibagaki Y**, Tai C, Nayak A, Wahba I. Intra-abdominal hypertension is an under-appreciated cause of acute renal failure. *Nephrol Dial Transplant* 2006; **21**: 3567-3570 [PMID: 16935902 DOI: 10.1093/ndt/gfl496]
38 **Better OS**, Abassi ZA. Early fluid resuscitation in patients with rhabdomyolysis. *Nat Rev Nephrol* 2011; **7**: 416-422 [PMID: 21587227 DOI: 10.1038/nrneph.2011.56]
39 **Holm C**, Melcer B, Hörbrand F, Wörl H, von Donnersmarck GH, Mühlbauer W. Intrathoracic blood volume as an end point in resuscitation of the severely burned: an observational study of 24 patients. *J Trauma* 2000; **48**: 728-734 [PMID: 10780609 DOI: 10.1097/00005373-200004000-00023]
40 **Penn AS**, Rowland LP, Fraser DW. Drugs, coma, and myoglobinuria. *Arch Neurol* 1972; **26**: 336-343 [PMID: 5015592 DOI: 10.1001/archneur.1972.00490100066006]
41 **Szewczyk D**, Ovadia P, Abdullah F, Rabinovici R. Pressure-induced rhabdomyolysis and acute renal failure. *J Trauma* 1998; **44**: 384-388 [PMID: 9498517 DOI: 10.1097/00005373-199802000-00028]
42 **Biswas S**, Gnanasekaran I, Ivatury RR, Simon R, Patel AN. Exaggerated lithotomy position-related rhabdomyolysis. *Am Surg* 1997; **63**: 361-364 [PMID: 9124760]

P- Reviewers: Al-Benna S, Jeschke M
S- Editor: Zhai HH **L- Editor**: Wang TQ **E- Editor**: Liu XM

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.8

World J Crit Care Med 2014 February 4; 3(1): 8-14
ISSN 2220-3141 (online)

EDITORIAL

Iatrogenic pneumothorax related to mechanical ventilation

Chien-Wei Hsu, Shu-Fen Sun

Chien-Wei Hsu, Shu-Fen Sun, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan
Chien-Wei Hsu, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan
Shu-Fen Sun, Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan
Author contributions: Hsu CW and Sun SF contributed to this paper, including designing, drafting and revising the article and giving final approval.
Correspondence to: Chien-Wei Hsu, MD, Assistant Professor, Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung 813, Taiwan. cwhsu2003@yahoo.com
Telephone: + 886-7-342121-2081 Fax: +886-7-3420243
Received: June 25, 2013 Revised: October 30, 2013
Accepted: November 18, 2013
Published online: February 4, 2014

Abstract

Pneumothorax is a potentially lethal complication associated with mechanical ventilation. Most of the patients with pneumothorax from mechanical ventilation have underlying lung diseases; pneumothorax is rare in intubated patients with normal lungs. Tension pneumothorax is more common in ventilated patients with prompt recognition and treatment of pneumothorax being important to minimize morbidity and mortality. Underlying lung diseases are associated with ventilator-related pneumothorax with pneumothoraces occurring most commonly during the early phase of mechanical ventilation. The diagnosis of pneumothorax in critical illness is established from the patients' history, physical examination and radiological investigation, although the appearances of a pneumothorax on a supine radiograph may be different from the classic appearance on an erect radiograph. For this reason, ultrasonography is beneficial for excluding the diagnosis of pneumothorax. Respiration-dependent movement of the visceral pleura and lung surface with respect to the parietal pleura and chest wall can be easily visualized with transthoracic sonography given that the presence of air in the pleural space prevents sonographic visualization of visceral pleura movements. Mechanically ventilated patients with a pneumothorax require tube thoracostomy placement because of the high risk of tension pneumothorax. Small-bore catheters are now preferred in the majority of ventilated patients. Furthermore, if there are clinical signs of a tension pneumothorax, emergency needle decompression followed by tube thoracostomy is widely advocated. Patients with pneumothorax related to mechanical ventilation who have tension pneumothorax, a higher acute physiology and chronic health evaluation Ⅱ score or PaO_2/FiO_2 < 200 mmHg were found to have higher mortality.

Key words: Barotrauma; Complication; Critical care; Mechanical ventilation; Pneumothorax

Core tip: Patients with pneumothorax related to mechanical ventilation (PRMV) have a high mortality rate. PRMV often occurs in the early stage of mechanical ventilation and it may recur on the other side of lung in a short period of time. Low compliance is associated with a high incidence of PRMV, with PRMV being more related to the underlying process than the ventilatory setting. PRMV patients with tension pneumothorax, higher acute physiology and chronic health evaluation score or PaO_2/FiO_2 < 200 mmHg have a higher mortality.

Hsu CW, Sun SF. Iatrogenic pneumothorax related to mechanical ventilation. *World J Crit Care Med* 2014; 3(1): 8-14 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/8.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.8

INTRODUCTION

Pneumothorax, defined as the presence of air in the pleural space, is a serious complication of mechanical ventilation and is associated with increased morbid-

ity and mortality[1,2]. Pneumothorax can be categorized as primary, secondary, iatrogenic or traumatic according to etiology. Mechanical ventilation was found to be the common cause of iatrogenic pneumothorax in an intensive care unit (ICU)[3]. Pneumothorax is rare in intubated patients with normal lungs and most patients with pneumothorax related to mechanical ventilation (PRMV) have underlying lung diseases that range from primary obstructive lung disease to secondary pneumonia and acute respiratory distress syndrome (ARDS)[4-6]. In critical illness, pneumothoraces may be difficult to diagnose when they have different clinical presentations and their locations are atypical and complicated by other disease processes in unconscious patients[7,8]. Prompt recognition and treatment of pneumothorax is important to minimize morbidity and mortality[9] because if pneumothorax is not diagnosed quickly, once tension pneumothorax ensues, it usually has a malignant course leading to death if untreated[10]. Sudden fall in oxygen saturation followed by hypotension are often observed clinically in these patients[11,12]. Tension pneumothorax is more common in ventilated patients, occurring in 30%-97% percent of all pneumothoraces[13-17].

Pneumothorax was found to be an independent predictor of mortality during mechanical ventilation[18] and was associated with a significant increase in the ICU length of stay, hospital stay and mortality in all mechanically ventilated patients[3]. The mortality rates are high, ranging from 46% to 77% if barotrauma is a complication of mechanical ventilation[2,3,14,15,19-24].

EPIDEMIOLOGY

Patients who received mechanical ventilation have an approximate incidence of barotrauma of 4%-15%[4,13,19,25]. It has been reported that a 14%-87% incidence of pneumothorax occurs depending on severity and duration of ARDS and mode of ventilator for management[1,21,26]. A prior study found that the incidence rate of pneumothorax decreased after the implementation of protective lung strategies in pediatric patients with severe ARDS[27]. The incidence of barotrauma has been reported to be as low as 0.5% in postoperative patients[23].

DISEASE ASSOCIATED WITH PNEUMOTHORAX

Development of pneumothorax is most closely correlated with underlying lung disease[1,21]. Pneumonia is an important predisposing factor in the development of pulmonary barotrauma in mechanically ventilated patients[28]. Necrotizing bacterial pneumonia can cause air leaks into the pleura that result in development of pneumothorax[29].

Chronic obstructive pulmonary disease and asthma are also common underlying diseases associated with pneumothorax. High airway pressures are required to overcome severe bronchial obstruction. However, because of a variability of obstruction in the different airways, there is a mal-distribution of mechanical tidal volume, which promotes gas trapping and non-uniform alveolar distension. That is why these patients are at risk of pneumothorax[30].

PRMV is most closely correlated with ARDS[31], a heterogeneous disease in which the lung is physiologically small and with low compliance[32]. The dependent lung regions tend to be collapsed and the lung regions subject to high pressure overinflation and alveolar rupture are nondependent regions when positive end-expiratory pressure (PEEP) inflates and recruits some of collapsed regions during mechanical ventilation[33,34]. Subpleural and intrapulmonary air cysts occur in ARDS patients and the rupture of these air cysts may be a cause of pneumothorax[14]. Whether the pneumothorax in ARDS arises from overinflation of normal lung regions or from cyst rupture has not yet been conclusively established[21].

Other diseases such as lung cancer, tuberculosis, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis X, Marfan's syndrome, Ehlers-Danlos syndrome, lymphangioleiomyomatosis, rheumatoid arthritis and other connective tissue disease may predispose to the development of a pneumothorax[35].

PATHOPHYSIOLOGY AND RISK FACTORS FOR PRMV

An early investigation reported that peak airway pressure over 50 cm H_2O is associated with increased risk of alveolar rupture during mechanical ventilation[4]. There have also been correlations made between high peak airway pressure and the development of pneumothorax[15,36]. High PEEP had been reported to be associated with pneumothorax[1] but several studies have found no such relationship[15,17,23,28,37]. Increased pressure is not enough by itself to produce alveolar rupture, with some studies demonstrating that pneumothorax is related to high tidal volume[37]. In animal studies, there is evidence to conclude that lung overdistension rather than high airway pressure is the primary cause of alveolar and interstitial injury[38,39].

A clinical study showed that when plateau pressure was maintained lower than 35 cm H_2O, pneumothorax was unavoidable[40]. Although one study showed that the incidence of pneumothorax decreased after implementation of protective lung strategies[27], several recent studies comparing low tidal volume with conventional ventilation in ARDS failed to demonstrate any reduction in barotrauma when low tidal volumes were used[41-43]. Previous literature showed the incidence of barotrauma did not relate to the ventilatory settings[22,31,41,44] but a low compliance was associated with a high incidence of barotrauma, which suggested that barotrauma has been more related to the underlying process than the ventilatory setting[40].

CLINICAL MANIFESTATIONS OF PRMV

Pneumothorax is secondary to ruptured alveoli and dis-

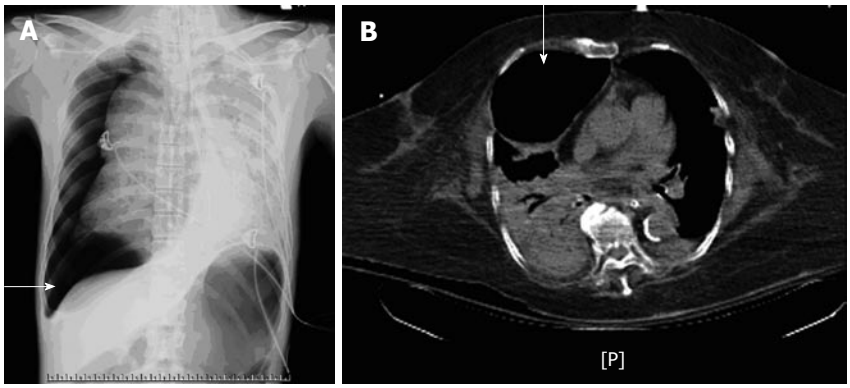


Figure 1 A chest radiograph demonstrates (A) and computed tomography (B) right pneumothorax (arrows). Air may lie in the costophrenic angle extending more inferiorly than usual (A, arrow).

section of air along the vascular sheaths passing to the mediastinum, subcutaneous tissue and retroperitoneum. Therefore, it may manifest as pulmonary interstitial emphysema, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema[32]. Patients may present with tachycardia, chest pain, tachypnea, agitation, hypotension, cyanosis or consciousness change. Tachycardia is the most common finding.

It has been observed that the median time from mechanical ventilation to the development of pneumothorax was 4 d[3]. Anzueto *et al*[45] reported that 80% of their patients developed pneumothorax within the first 3 d of mechanical ventilation. Gattinoni *et al*[21] found that late ARDS (> 2 wk of mechanical ventilation) patients had an increased incidence of pneumothoraces when compared to early ARDS (less than 1 wk of mechanical ventilation) patients[21]. However, Gammon *et al*[31] reported that pneumothoraces occurred most commonly during the early phase of ARDS, with a declining risk over time.

Approximately 7.4%-10% of patients with first episode pneumothorax will develop second episode pneumothorax on the other lung during mechanical ventilation[3,31]. Clinically, we should take notice of these patients because the pneumothorax might attack the lung on the other side.

Tension pneumothorax is common in mechanically ventilated patients[13-17]. Mechanical ventilation will increase gas flow through pleura defects, allowing more air to pass per unit time, and resulting in a more rapid intrapleural pressure rise with earlier mechanical compressive effects and rapid progress to cardiorespiratory collapse and death[46].

DIAGONOSIS

The diagnosis of pneumothorax in critical illness is established from patients' history, physical examination and radiological investigation. The factors related to the underlying lung disease are important in the history. Examination of the respiratory and cardiovascular systems may help establish the diagnosis of pneumothorax. However, examination findings may vary according to the size of pneumothorax and presence of limited cardiorespiratory reserve[47], with patients with a small pneumothorax (one involving < 15% of the hemithorax) possibly having a normal physical examination. Careful inspection and repeated auscultation of the chest is therefore crucial. Contralateral tracheal deviation, hyperresonant percussion over the chest and decreased breathing sounds might be noted. Reduction in tidal volume during pressure controlled ventilation and increased airway pressure with volume controlled ventilation might be found from ventilators. A pulsus paradoxus on the arterial trace and increased central venous pressure from central venous catheterization may be observed[8,9,46,47].

It should be noted that many of the above findings are nonspecific and have not been a reliable indicator of pneumothorax given that dyspnea severity can be out of proportion to the size of the pneumothorax. The radiographic data thus remains the gold standard for the diagnosis of pneumothorax[8]. The chest radiograph may show radiolucent hemithorax with apparent lung edge and absent lung marking. Mediastinal emphysema was the initial manifestation of extra-alveolar air[1]. Although an erect posteroanterior chest radiograph may help to estimate the pneumothorax size[48], it is not practical in critical illness. However, the supine anteroposterior chest radiographs are available in the ICU, although the appearances of a pneumothorax on a supine radiograph may be different from the classic appearances on an erect radiograph. Air may lie in the costophrenic angle extending more inferiorly than usual (Figure 1A), which has been called deep sulcus sign[49]. Concurrent lung disease may lead to different distributions of free air in the pleural space than in relatively normal lungs[50] or it may lead to loculated gas collections if there is associated pleural disease[51]. Some radiographic findings that may be confused with pneumothorax are skin folds, visceral gas within the gas and emphysema bullae. A chest computed tomography (CT) examination, in contrast, can differentiate these diagnoses and is the gold standard test for both the diagnosis and sizing of pneumothorax (Figure 1B)[52]. CT is an excellent tool to differentiate bullous lung disease and prevent unnecessary drainage attempts that may result in the creation of a parenchymal-pleural fistula[53]. Chest radiographs may not distinguish between emphysematous bullae and pneumothorax, thus possibly resulting in potentially catastrophic insertion of intercostal chest drain into emphysematous bullae in mechanically ventilated patients. Unfortunately, it is not always practical or safe

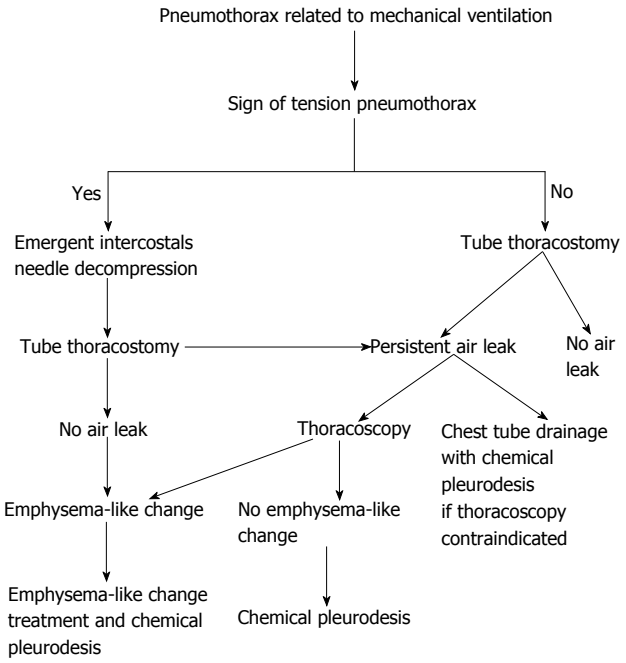


Figure 2 An algorithmic approach to treatment of pneumothorax related to mechanical ventilation.

to transport critically ill patients for a CT scan to exclude pneumothorax, particularly when the patient is hemodynamically unstable.

Transthoracic sonography is a diagnostic tool for pneumothorax[54-56]. There are several advantages of ultrasonography over standard chest radiography and CT scanning, including the lower radiation, portability, real-time imaging and the ability to easily perform dynamic and repeat evaluation. The main use of ultrasonography for assessment of pneumothorax lies in its capacity to rule out a pneumothorax. Respiration-dependent movement of the visceral pleura and lung surface with respect to the parietal pleura and chest wall can be easily visualized with real-time transthoracic sonography. This characteristic is known as lung sliding or gliding sign[56-58]. At the boundary between the pleura and the ventilated lung, intensive band-like reverberation echoes (comet-tail artifacts) are evoked during breathing movement[54,57]. M-mode images of patients without pneumothorax show breath-dependent movements as a single, thin comet-tail artifact. The presence of air in the pleural space prevents sonographic visualization of visceral pleura movements and the gliding sign and comet-tail artifacts disappear[57,58]. M-mode images of patients with pneumothorax show the immobility of these artifacts known as frozen echoes under breathing movement.

One study showed transthoracic ultrasound was more sensitive than chest radiography in the detection of pneumothorax[59]. Another study comparing ultrasonography to CT scan and chest radiographs for diagnosis of occult pneumothorax revealed that the use of ultrasonography detected 92% of occult pneumothoraces diagnosed with CT scan[60]. In trained hands, an ultrasound examination may obviate the need for empiric tube thoracostomy for suspected tension pneumothorax.

TREATMENT AND PREVENTION

Most mechanically ventilated patients with a pneumothorax require tube thoracostomy placement because of the high risk of tension pneumothorax[61]. The strategy of managing pneumothorax is shown in Figure 2. It is not advisable to wait for a radiograph if there are clinical signs of a tension pneumothorax. Emergency needle decompression followed by tube thoracostomy is widely advocated[46]. In critically ill patients with minimal pulmonary reserve, even a small pneumothorax can have adverse cardiopulmonary effects[62]. Positive pressure ventilation can exacerbate air leaks and prevent pleural healing, potentially causing a rapid increase in the size and severity of existing pneumothorax.

The traditional treatment for pneumothorax in mechanically ventilated patients has been chest tube thoracostomy[61], an image-guided small catheter whose size ranges from 7 to 10 Fr, to become an effective therapeutic option for pneumothorax[63]. A retrospective review of 62 ventilated patients who underwent small-bore chest tube drainage as the primary management of pneumothorax found a 68.6% success rate, defined as no residual air seen in the follow-up chest radiograph, and with no major complications[64]. These results compare favorably with previous data showing a success rate of 55% with the same definition for success as in the previous study with a large bore tube[20].

In patients with a persistent air leak or failure of the lung to expand, early thoracic surgical consultation is generally requested within 3-5 d[65]. Although surgical intervention is considered very effective and safe with a low recurrence rate, the studies reaching this conclusion do not include critically ill patients[66,67].

Muscle relaxants might be effective to decrease the incidence of pneumothorax for patients with ARDS. A recent study by Papazian *et al*[68] reported a significant reduction in pneumothoraces in patients with severe ARDS who received 48 h of paralysis.

OUTCOMES

Mechanically ventilated patients with pneumothorax had a significantly higher mortality rate than those without pneumothorax. de Lassence *et al*[3] reported that iatrogenic pneumothorax was associated with a greater than twofold increase in the risk of death. In terms of iatrogenic pneumothorax, the mortality rate of patients with ventilator-related pneumothorax was significantly higher than that of patients with procedure-related pneumothorax[20]. Ventilator-related pneumothorax patients with tension pneumothorax had a higher risk of death[20].

CONCLUSION

Pneumothorax is a medical emergency and a disease with a high mortality rate; it requires a careful awareness,

prompt recognition and intervention to reduce morbidity and mortality. Most patients with PRMV have underlying pulmonary diseases, the most common of which are pneumonia, ARDS and obstructive lung disease. Pneumothorax presentation and radiographic findings may be subtle or atypical. Whereas a CT scan is the gold standard for diagnosis, the use of ultrasonography has benefits in both diagnosis and management of pneumothorax. Most of the ventilated patients with a pneumothorax require immediate treatment with tube thoracostomy because of the high risk of progression to a tension pneumothorax. Small-bore catheters are now preferred in the majority of ventilated patients.

REFERENCES

1 **Gammon RB**, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest* 1992; **102**: 568-572 [PMID: 1643949 DOI: 10.1378/chest.102.2.568]

2 **Schnapp LM**, Chin DP, Szaflarski N, Matthay MA. Frequency and importance of barotrauma in 100 patients with acute lung injury. *Crit Care Med* 1995; **23**: 272-278 [PMID: 7867352]

3 **de Lassence A**, Timsit JF, Tafflet M, Azoulay E, Jamali S, Vincent F, Cohen Y, Garrouste-Orgeas M, Alberti C, Dreyfuss D. Pneumothorax in the intensive care unit: incidence, risk factors, and outcome. *Anesthesiology* 2006; **104**: 5-13 [PMID: 16394682]

4 **Petersen GW**, Baier H. Incidence of pulmonary barotrauma in a medical ICU. *Crit Care Med* 1983; **11**: 67-69 [PMID: 6337021 DOI: 10.1097/00003246-19830202000-00002]

5 **Pierson DJ**. Complications associated with mechanical ventilation. *Crit Care Clin* 1990; **6**: 711-724 [PMID: 2199002]

6 **Parker JC**, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. *Crit Care Med* 1993; **21**: 131-143 [PMID: 8420720 DOI: 10.1097/00003246-199301000-00024]

7 **Tocino IM**, Miller MH, Fairfax WR. Distribution of pneumothorax in the supine and semirecumbent critically ill adult. *AJR Am J Roentgenol* 1985; **144**: 901-905 [PMID: 3872573 DOI: 10.2214/ajr.144.5.901]

8 **Rankine JJ**, Thomas AN, Fluechter D. Diagnosis of pneumothorax in critically ill adults. *Postgrad Med J* 2000; **76**: 399-404 [PMID: 10878196 DOI: 10.1136/pmj.76.897.399]

9 **Yarmus L**, Feller-Kopman D. Pneumothorax in the critically ill patient. *Chest* 2012; **141**: 1098-1105 [PMID: 22474153 DOI: 10.1378/chest.11-1691]

10 **Rojas R**, Wasserberger J, Balasubramaniam S. Unsuspected tension pneumothorax as a hidden cause of unsuccessful resuscitation. *Ann Emerg Med* 1983; **12**: 411-412 [PMID: 6859647 DOI: 10.1016/S0196-0644(83)80502-2]

11 **Coats TJ**, Wilson AW, Xeropotamous N. Pre-hospital management of patients with severe thoracic injury. *Injury* 1995; **26**: 581-585 [PMID: 8550162 DOI: 10.1016/0020-1383(95)00107-K]

12 **Deakin CD**, Davies G, Wilson A. Simple thoracostomy avoids chest drain insertion in prehospital trauma. *J Trauma* 1995; **39**: 373-374 [PMID: 7674410 DOI: 10.1097/00005373-199508000-00031]

13 **Zwillich CW**, Pierson DJ, Creagh CE, Sutton FD, Schatz E, Petty TL. Complications of assisted ventilation. A prospective study of 354 consecutive episodes. *Am J Med* 1974; **57**: 161-170 [PMID: 4843890 DOI: 10.1016/0002-9343(74)90440-9]

14 **Rohlfing BM**, Webb WR, Schlobohm RM. Ventilator-related extra-alveolar air in adults. *Radiology* 1976; **121**: 25-31 [PMID: 1066716]

15 **Woodring JH**. Pulmonary interstitial emphysema in the adult respiratory distress syndrome. *Crit Care Med* 1985; **13**: 786-791 [PMID: 3896647 DOI: 10.1097/00003246-198510000-00003]

16 **Johnson TH**, Altman AR. Pulmonary interstitial gas: first sign of barotrauma due to PEEP therapy. *Crit Care Med* 1979; **7**: 532-535 [PMID: 389555 DOI: 10.1097/00003246-197912000-00004]

17 **Zimmerman JE**, Dunbar BS, Klingenmaier CH. Management of subcutaneous emphysema, pneumomediastinum, and pneumothorax during respirator therapy. *Crit Care Med* 1975; **3**: 69-73 [PMID: 1157510 DOI: 10.1097/00003246-197503000-00004]

18 **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]

19 **de Latorre FJ**, Tomasa A, Klamburg J, Leon C, Soler M, Rius J. Incidence of pneumothorax and pneumomediastinum in patients with aspiration pneumonia requiring ventilatory support. *Chest* 1977; **72**: 141-144 [PMID: 884974 DOI: 10.1378/chest.72.2.141]

20 **Chen KY**, Jerng JS, Liao WY, Ding LW, Kuo LC, Wang JY, Yang PC. Pneumothorax in the ICU: patient outcomes and prognostic factors. *Chest* 2002; **122**: 678-683 [PMID: 12171850 DOI: 10.1378/chest.122.2.678]

21 **Gattinoni L**, Bombino M, Pelosi P, Lissoni A, Pesenti A, Fumagalli R, Tagliabue M. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994; **271**: 1772-1779 [PMID: 8196122 DOI: 10.1001/jama.1994.03510460064035]

22 **Weg JG**, Anzueto A, Balk RA, Wiedemann HP, Pattishall EN, Schork MA, Wagner LA. The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; **338**: 341-346 [PMID: 9449726 DOI: 10.1056/NEJM199802053380601]

23 **Cullen DJ**, Caldera DL. The incidence of ventilator-induced pulmonary barotrauma in critically ill patients. *Anesthesiology* 1979; **50**: 185-190 [PMID: 373507 DOI: 10.1097/00000542-197903000-00003]

24 **Fleming WH**, Bowen JC. Early complications of long-term respiratory support. *J Thorac Cardiovasc Surg* 1972; **64**: 729-738 [PMID: 4507848]

25 **Strange C**. Pleural complications in the intensive care unit. *Clin Chest Med* 1999; **20**: 317-327 [PMID: 10386259]

26 **Jantz MA**, Pierson DJ. Pneumothorax and barotrauma. *Clin Chest Med* 1994; **15**: 75-91 [PMID: 8200194]

27 **Miller MP**, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS. *Chest* 2008; **134**: 969-973 [PMID: 18689581 DOI: 10.1378/chest.08-0743]

28 **Kumar A**, Pontoppidan H, Falke KJ, Wilson RS, Laver MB. Pulmonary barotrauma during mechanical ventilation. *Crit Care Med* 1973; **1**: 181-186 [PMID: 4587509 DOI: 10.1097/00003246-197307000-00001]

29 **Fukagawa T**. Centromere DNA, proteins and kinetochore assembly in vertebrate cells. *Chromosome Res* 2004; **12**: 557-567 [PMID: 15289663 DOI: 10.1177/0885066602239120]

30 **Marcy TW**. Barotrauma: detection, recognition, and management. *Chest* 1993; **104**: 578-584 [PMID: 8339650 DOI: 10.1378/chest.104.2.578]

31 **Gammon RB**, Shin MS, Groves RH, Hardin JM, Hsu C, Buchalter SE. Clinical risk factors for pulmonary barotrauma: a multivariate analysis. *Am J Respir Crit Care Med* 1995; **152**: 1235-1240 [PMID: 7551376 DOI: 10.1164/ajrccm.152.4]

32 **Gattinoni L**, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005; **31**: 776-784 [PMID: 15812622]

33 **Gattinoni L**, Mascheroni D, Torresin A, Marcolin R, Fumagalli R, Vesconi S, Rossi GP, Rossi F, Baglioni S, Bassi F. Morphological response to positive end expiratory pressure in

acute respiratory failure. Computerized tomography study. *Intensive Care Med* 1986; **12**: 137-142 [PMID: 3525633]
34 **Gattinoni L**, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni D. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. *Anesthesiology* 1988; **69**: 824-832 [PMID: 3057937 DOI: 10.1097/00000542-198812000-00005]
35 **Noppen M**, De Keukeleire T. Pneumothorax. *Respiration* 2008; **76**: 121-127 [PMID: 18708734 DOI: 10.1159/000135932]
36 **Haake R**, Schlichtig R, Ulstad DR, Henschen RR. Barotrauma. Pathophysiology, risk factors, and prevention. *Chest* 1987; **91**: 608-613 [PMID: 3549176 DOI: 10.1378/chest.91.4.608]
37 **Steier M**, Ching N, Roberts EB, Nealon TF. Pneumothorax complicating continuous ventilatory support. *J Thorac Cardiovasc Surg* 1974; **67**: 17-23 [PMID: 4203001]
38 **Dreyfuss D**, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998; **157**: 294-323 [PMID: 9445314 DOI: 10.1164/ajrccm.157.1.9604014]
39 **Dreyfuss D**, Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Med* 1992; **18**: 139-141 [PMID: 1644960 DOI: 10.1007/BF01709236]
40 **Boussarsar M**, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med* 2002; **28**: 406-413 [PMID: 11967593]
41 **Brochard L**, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, Clémenti E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; **158**: 1831-1838 [PMID: 9847275 DOI: 10.1164/ajrccm.158.6.9801044]
42 **Stewart TE**, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med* 1998; **338**: 355-361 [PMID: 9449728 DOI: 10.1056/NEJM199802053380603]
43 **Brower RG**, Shanholtz CB, Fessler HE, Shade DM, White P, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; **27**: 1492-1498 [PMID: 10470755 DOI: 10.1097/00003246-199508000-00015]
44 **Morris AH**, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Weaver LK, Dean NC, Thomas F, East TD, Pace NL, Suchyta MR, Beck E, Bombino M, Sittig DF, Böhm S, Hoffmann B, Becks H, Butler S, Pearl J, Rasmusson B. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; **149**: 295-305 [PMID: 8306022 DOI: 10.1164/ajrccm.149.2.8306022]
45 **Anzueto A**, Frutos-Vivar F, Esteban A, Alía I, Brochard L, Stewart T, Benito S, Tobin MJ, Elizalde J, Palizas F, David CM, Pimentel J, González M, Soto L, D'Empaire G, Pelosi P. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med* 2004; **30**: 612-619 [PMID: 14991090 DOI: 10.1007/s00134-004-2187-7]
46 **Leigh-Smith S**, Harris T. Tension pneumothorax--time for a re-think? *Emerg Med J* 2005; **22**: 8-16 [PMID: 15611534 DOI: 10.1136/emj.2003.010421]
47 **Currie GP**, Alluri R, Christie GL, Legge JS. Pneumothorax: an update. *Postgrad Med J* 2007; **83**: 461-465 [PMID: 17621614 DOI: 10.1136/pmj.2007.056978]
48 **Noppen M**, Alexander P, Driesen P, Slabbynck H, Verstraete A. Quantification of the size of primary spontaneous pneumothorax: accuracy of the Light index. *Respiration* 2001; **68**: 396-399 [PMID: 11464087 DOI: 10.1159/000050533]
49 **Chiles C**, Ravin CE. Radiographic recognition of pneumothorax in the intensive care unit. *Crit Care Med* 1986; **14**: 677-680 [PMID: 3720324 DOI: 10.1097/00003246-198608000-00002]
50 **Gobien RP**, Reines HD, Schabel SI. Localized tension pneumothorax: unrecognized form of barotrauma in adult respiratory distress syndrome. *Radiology* 1982; **142**: 15-19 [PMID: 7031759]
51 **Gordon R**. The deep sulcus sign. *Radiology* 1980; **136**: 25-27 [PMID: 7384513]
52 **Kelly AM**, Weldon D, Tsang AY, Graham CA. Comparison between two methods for estimating pneumothorax size from chest X-rays. *Respir Med* 2006; **100**: 1356-1359 [PMID: 16406560 DOI: 10.1016/j.rmed.2005.11.022]
53 **Phillips GD**, Trotman-Dickenson B, Hodson ME, Geddes DM. Role of CT in the management of pneumothorax in patients with complex cystic lung disease. *Chest* 1997; **112**: 275-278 [PMID: 9228391 DOI: 10.1378/chest.112.1.275]
54 **Wernecke K**, Galanski M, Peters PE, Hansen J. Pneumothorax: evaluation by ultrasound--preliminary results. *J Thorac Imaging* 1987; **2**: 76-78 [PMID: 3298684]
55 **Targhetta R**, Bourgeois JM, Chavagneux R, Marty-Double C, Balmes P. Ultrasonographic approach to diagnosing hydropneumothorax. *Chest* 1992; **101**: 931-934 [PMID: 1555465 DOI: 10.1378/chest.101.4.931]
56 **Targhetta R**, Bourgeois JM, Chavagneux R, Coste E, Amy D, Balmes P, Pourcelot L. Ultrasonic signs of pneumothorax: preliminary work. *J Clin Ultrasound* 1993; **21**: 245-250 [PMID: 8478457 DOI: 10.1002/jcu.1870210406]
57 **Wernecke K**. Ultrasound study of the pleura. *Eur Radiol* 2000; **10**: 1515-1523 [PMID: 11044919 DOI: 10.1007/s003300000526]
58 **Reissig A**, Kroegel C. Accuracy of transthoracic sonography in excluding post-interventional pneumothorax and hydropneumothorax. Comparison to chest radiography. *Eur J Radiol* 2005; **53**: 463-470 [PMID: 15741021 DOI: 10.1016/j.ejrad.2004.04.014]
59 **Jalli R**, Sefidbakht S, Jafari SH. Value of ultrasound in diagnosis of pneumothorax: a prospective study. *Emerg Radiol* 2013; **20**: 131-134 [PMID: 23179505 DOI: 10.1007/s10140-012-1091-7]
60 **Soldati G**, Testa A, Sher S, Pignataro G, La Sala M, Silveri NG. Occult traumatic pneumothorax: diagnostic accuracy of lung ultrasonography in the emergency department. *Chest* 2008; **133**: 204-211 [PMID: 17925411 DOI: 10.1378/chest.07-1595]
61 **Gilbert TB**, McGrath BJ, Soberman M. Chest tubes: indications, placement, management, and complications. *J Intensive Care Med* 1993; **8**: 73-86 [PMID: 10148363]
62 **Marcy TW**, Marini JJ. Respiratory distress in the ventilated patient. *Clin Chest Med* 1994; **15**: 55-73 [PMID: 8200193]
63 **Chon KS**, vanSonnenberg E, D'Agostino HB, O'Laoide RM, Colt HG, Hart E. CT-guided catheter drainage of loculated thoracic air collections in mechanically ventilated patients with acute respiratory distress syndrome. *AJR Am J Roentgenol* 1999; **173**: 1345-1350 [PMID: 10541116 DOI: 10.2214/ajr.173.5]
64 **Lin YC**, Tu CY, Liang SJ, Chen HJ, Chen W, Hsia TC, Shih CM, Hsu WH. Pigtail catheter for the management of pneumothorax in mechanically ventilated patients. *Am J Emerg Med* 2010; **28**: 466-471 [PMID: 20466227 DOI: 10.1016/j.ajem.2009.01.033]
65 **MacDuff A**, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010; **65** Suppl 2: ii18-ii31 [PMID: 20696690 DOI: 10.1136/thx.2010.136986]

66 **Hatz RA**, Kaps MF, Meimarakis G, Loehe F, Müller C, Fürst H. Long-term results after video-assisted thoracoscopic surgery for first-time and recurrent spontaneous pneumothorax. *Ann Thorac Surg* 2000; **70**: 253-257 [PMID: 10921718 DOI: 10.1016/S0003-4975(00)01411-9]
67 **Thomas P**, Le Mee F, Le Hors H, Sielezneff I, Auge A, Giudicelli R, Fuentes P. [Results of surgical treatment of persistent or recurrent pneumothorax]. *Ann Chir* 1993; **47**: 136-140 [PMID: 8317871]
68 **Papazian L**, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107-1116 [PMID: 20843245 DOI: 10.1056/NEJMoa1005372]

P- Reviewers: Kastelik JA, Kawai H **S- Editor**: Zhai HH
L- Editor: Roemmele A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.15

World J Crit Care Med 2014 February 4; 3(1): 15-23
ISSN 2220-3141 (online)

REVIEW

Disaster preparedness, pediatric considerations in primary blast injury, chemical, and biological terrorism

Mitchell Hamele, William Bradley Poss, Jill Sweney

Mitchell Hamele, W Bradley Poss, Jill Sweney, Division of Pediatric Critical Care, Department of Pediatrics, School of Medicine, University of Utah, Salt Lake City, UT 84108, United States
Author contributions: Hamele M, Poss WB and Sweney J contributed equally to this manuscript.
Correspondence to: Mitchell Hamele, MD, Division of Pediatric Critical Care, Department of Pediatrics, School of Medicine, University of Utah, 295 Chipeta Way, Salt Lake City, UT 84108, United States. Mitchell.Hamele@hsc.utah.edu
Telephone: +1-801-5877572 Fax: +1-801-5818686
Received: September 15, 2013 Revised: November 21, 2013
Accepted: December 9, 2013
Published online: February 4, 2014

Abstract

Both domestic and foreign terror incidents are an unfortunate outgrowth of our modern times from the Oklahoma City bombings, Sarin gas attacks in Japan, the Madrid train bombing, anthrax spores in the mail, to the World Trade Center on September 11th, 2001. The modalities used to perpetrate these terrorist acts range from conventional weapons to high explosives, chemical weapons, and biological weapons all of which have been used in the recent past. While these weapons platforms can cause significant injury requiring critical care the mechanism of injury, pathophysiology and treatment of these injuries are unfamiliar to many critical care providers. Additionally the pediatric population is particularly vulnerable to these types of attacks. In the event of a mass casualty incident both adult and pediatric critical care practitioners will likely be called upon to care for children and adults alike. We will review the presentation, pathophysiology, and treatment of victims of blast injury, chemical weapons, and biological weapons. The focus will be on those injuries not commonly encountered in critical care practice, primary blast injuries, category A pathogens likely to be used in terrorist incidents, and chemical weapons including nerve agents, vesicants, pulmonary agents, cyanide, and riot control agents with special attention paid to pediatric specific considerations.

Key words: Terrorism; Bioterrorism; Chemical terrorism; Blast injuries; Mass casualty incidents; Disasters; Pediatrics

Core tip: Terrorism and mass casualty events continue to increase on a global scale. Many injuries specific to terrorist incidents including blast injury, biological, and chemical casualties are unfamiliar to the critical care provider. We review the presentation, pathophysiology and care of these casualties. We give specific consideration to the pediatric population as they are a particularly vulnerable population and both adult and pediatric critical care specialists would be called upon to care for children in the event of a massive casualty terrorist event.

Hamele M, Poss WB, Sweney J. Disaster preparedness, pediatric considerations in primary blast injury, chemical, and biological terrorism. *World J Crit Care Med* 2014; 3(1): 15-23 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/15.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.15

INTRODUCTION

Terrorism is an unfortunate fact of life in current times. Children have been identified as a specific vulnerable population[1]. Additionally children have increased mortality when exposed to combat injury[2]. While these events have increased in frequency, exposure during medical training is limited. This review will cover those aspects of care of the pediatric victim of terrorist incidents that may not be familiar to the critical care provider. We will cover primary blast injury (PBI), biological weapons, and chemical weapons.

Table 1 Pediatric specific vulnerabilities to terrorist attacks

Vulnerability	Blast Injury	Biological agents	Chemical agents
Proximity to ground		Agents settle to the ground	Agents tend to pool in lower areas
Increased minute ventilation		Increased exposure to inhaled agents	Increased exposure to inhaled agents
Provider unfamiliarity with pediatric dosing of medications		Dosing of antibiotics different	No prepackaged store of antidotes in pediatric doses
Lack of knowledge or inability to flee danger	Either unaware or unable to flee from explosion Potentially curious about ordinance	Unlikely to recognize signs/ symptoms of biologic agents	Would not know to flee from strange odor or seek medical help with symptoms
Lack of stockpile of pediatric dosed antidotes and vaccines		Prepackaged stockpiles of vaccines and antidotes not dosed for small children[32]	Lack of guidelines for dosing of antidotes in children
Less blood volume/ physiologic reserve	More rapidly develop life threatening blood loss	Prone to dehydration with illness. Lower functional residual capacity	More prone to respiratory distress/ failure with nerve agents, vesicants, and pulmonary agents
Thinner skin			Faster absorbtion of agents
Increased BSA to mass ratio	Prone to hypothermia during triage, evacuation and treatment		Prone to hypothermia with decontamination
Developmental immaturity	Unable to follow mental status exam/communicate other injuries early	Present later in the course of biologic agents	Unable to promptly communicate symptoms
Increased head size compared to body	Increased head AIS when compared to adults[2]		

AIS: Abbreviated injury score; BSA: Body surface area.

High-order explosives (HE) were first available after dynamite was developed by Alfred Nobel in 1866. Since then several other HE have been developed and are used in up to 66% of terror attacks[3]. Biological warfare dates back to the Hittites driving diseased animals into enemy territories as early as 15th century BC. In 1346, Mongols hurled bodies of those killed by plague into Crimean city of Caffa, causing an epidemic resulting in their surrender. Chemical weapons were first used on a large scale during World War I where mustard, chlorine, and phosgene were used in the trenches[4]. In more recent times, Saddam Hussein and the Iraqi military used the nerve agent sarin against Kurdish villagers and the Iranian military during the Iraq-Iran War in 1988 with 75% of casualties being women and children. Sarin has been used on at least two occasions in the mid-1990s by the Japanese terror cult Aum Shinrikyo, including an incident in 1995 at a Tokyo subway station that killed 15 and injured over 5000. Among the injured were healthcare providers who were unprepared to deal with contaminated victims. Recent events in Syria have also clearly shown that chemical weapons are a threat we still face. Finally, chemical agents may be introduced into the food supply as was seen with the placement of a nicotine-containing insecticide into ground beef in Michigan, United States in 2002 that resulted in more than 40 children becoming ill.

As mentioned, children are identified as a vulnerable population. They have several specific physiologic, anatomic, and developmental differences from adults which make the particularly vulnerable (Table 1). In 2010 the National Commission on Children and Disasters reported that while children make up 25% of the United States population only 25% of EMS agencies and 6% of hospital emergency rooms have supplies and equipment to treat children[1]. This problem is likely more prevalent in the developing world where children make up a larger portion of the population. When planning and executing exercises and simulations of disaster events, including terrorist attacks, it is imperative that the unique aspects of treating children are taken into account[1].

PBI

Explosive charges can be divided into 2 types, HE, which cause a supersonic overpressure wave, or low-order explosives which are lower energy and do not cause an overpressure wave. Examples of HE include C-4, TNT, and ammonium nitrate, which was used in the bombing at the Murrah Federal Building in Oklahoma City.

Injuries caused by a blast can be divided into 4 categories; primary, secondary, tertiary, and quaternary. PBI is injury caused as a direct effect of overpressure caused by the blast wave itself passing through the tissues. Low-order explosives typically do not cause PBI due to the lack of an overpressure wave. Secondary blast injury is caused by fragments propelled by the explosion. These penetrating injuries are more easily identifiable and also more familiar to most physicians. Tertiary injuries are those injuries caused by displacement of the victim's body and are the result of impact on a surface such as fractures, traumatic brain injury (TBI), or abrasions. Quaternary injuries are burns and inhalation caused by the blast itself[5]. While we differentiate these 4 types of injury, injury in explosions is multi-mechanistic and can be difficult to determine individually[6]. We will focus on PBI as the penetrating, blunt, and thermal trauma associated with secondary, tertiary, and quaternary blast injuries are more familiar to the critical care physician. For pediatric

specific vulnerabilities in blast injury please see Table 1.

The overpressure wave that causes PBI does so through 2 mechanisms, stress and shear, which cause injuries by transmission of kinetic energy as the wave travels from tissue into air-filled organs[6,7]. Stress waves are longitudinal and cause "spalling", which can cause significant microvascular and tissue damage. Shear waves, are transverse and cause disruption of tissue attachments[7].

When explosions occur in closed environments, mortality is higher due to the blast wave reflecting off solid walls. In the Madrid subway bombings of 2004, 63% of patients who survived to intensive care unit admission were noted to have blast lung injury[8]. In a 1996 analysis of detonations in terrorist incidents in Israel, explosions occurring in enclosed spaces versus open air detonations had a higher rate of mortality (49.0% *vs* 7.8%) and higher incidence of primary blast injuries (77.5% *vs* 33.4%)[9].

Blast lung injury

Primary blast lung injury (PBLI) occurs in 3%-14% of blast survivors and is the most common fatal complication of initial survivors of blast injury[9,10]. Passage of the overpressure wave from tissue to the air filled alveoli causes disruption of the capillary alveolar interface resulting in pulmonary hemorrhage, pulmonary edema, pneumothorax, pulmonary fat embolus, or air embolus from arterio-venous fistulas[11]. The resultant clinical signs suggestive of PBLI are tachypnea, respiratory distress, cyanosis, and hemoptysis[7]. Chest radiographs may show bilateral central pulmonary infiltrates that are not always initially present on admission[12]. In a retrospective review from Israel all patients with PBLI had pulmonary infiltrates and hypoxia[12]. Thus PBLI should be strongly suspected in any patient with any of the above findings especially in the absence of evidence of other penetrating or blunt chest injury.

Treatment of PBLI should include maintaining patency of the airway, oxygenation, avoidance of overzealous fluid administration (which children are at increased risk of), and support of ventilation. Historically it has been taught that positive pressure ventilation should be avoided but in one series with excellent outcomes, 76% of patients required intubation and mechanical ventilation[12]. Additionally these patients are at high risk of pneumothoraces and prophylactic placement of chest tubes prior to intubation or transport should be considered[13]. Pulmonary hemorrhage should be treated with optimization of coagulation but if oxygenation cannot be maintained then positive pressure ventilation and selective ventilation of the non-involved lung is recommended. Permissive hypercapnia such as that used with acute respiratory distress syndrome has been recommended as a ventilatory strategy in PBLI patients[14]. Identification of air emboli by echocardiography, computed tomography (CT), or bronchoscopy is critical in PBLI as these are a frequently fatal. Thoracotomy on the affected side is the recommended treatment for non-traumatic air embolus but may not be effective in PBLI as there may be multiple sites of injury[15]. Therefore a more conservative approach would be to put the patient in a modified lateral decubitus position with the injured lung down or prone position.

Cardiovascular blast injury

The cardiovascular effects in victims of a blast can be complex. Secondary or tertiary injuries can cause cardiac contusion or tamponade. The stress of being in a blast can induce myocardial infarction in susceptible adults with pre-existing heart disease. Unique to blast injury is the observed phenomenon of bradycardia, apnea, and hypotension immediately following a blast[7]. Rat studies have demonstrated a similar response after a blast with a drop in systemic vascular resistance (SVR)[16]. The same authors found that when they performed a surgical vagotomy and administered atropine to rats subjected to blast that these effects were diminished suggesting a vagal response to the blast itself[17]. Some data indicate that atropine may be a useful adjunct in blast patients experiencing hemodynamic compromise[7]. Infants may be at increased risk of this vagally mediated bradycardia, apnea, and lack of compensatory increase in SVR due to immaturity of their sympathetic nervous system. Additionally, given the relative flexibility of the pediatric thoracic cage they are at increased risk for cardiac contusions.

Gastrointestinal blast injury

The pathophysiology of gastrointestinal (GI) tract PBI is similar to PBLI. It occurs when the overpressure wave passes from tissue into gas filled spaces causing microvascular damage and tearing across tissue planes. Incidence ranges from 3.0%-6.7% amongst initial survivors in a series of 1040 patients[18]. The regions most affected were the terminal ileum and cecum[18]. Solid organs can rupture although this occurs less frequently. Signs and symptoms include those typically seen with abdominal hemorrhage and perforation to include, abdominal pain, nausea, emesis, hematemesis, melena, hypotension, or signs of peritoneal irritation and may present several hours to days after injury[7].

Diagnosis is primarily clinical and accomplished through serial exams, which can be more challenging in the pediatric population. Adjunctive diagnostic tests such as plain abdominal radiograph can help in diagnosis. Abdominal CT scan is very effective at demonstrating solid organ injury but may not be as sensitive with intestinal injury. Diagnostic peritoneal lavage can be used as an adjunct if other studies or clinical exam are not conclusive[18]. The treatment of GI blast injury is similar to that of blunt or penetrating abdominal injury and indications for surgical intervention are similar[18]. It should be noted that GI blast injury typically develops over several hours to days and that treatment of PBLI, cardiac injury and other life threatening injuries should be stabilized prior to treatment of the GI injuries if they are not life threatening.

Blast TBI

While blast TBI (bTBI) is a common occurrence in explosions there is also a high incidence of closed TBI due to tertiary blast injury making it difficult to separate the

Table 2 Management of chemical agents

Agent	Pediatric dosing	Notes
Nerve agents	Atropine 0.05 mg/kg *iv* or *im* q 2-5 min (max 5 mg) Pralidoxime 25 mg/kg *iv* or *im* q 1 h (max 1 g *iv* or 2 g *im*) Benzodiazepines: Midazolam *im* 0.2 mg/kg (max 10 mg) (1st choice) Lorazepam *iv*/*im* 0.1 mg/kg (max 4 mg) Diazepam *iv* 0.3 mg/kg (max 10 mg)	Atropine should be repeated for persistent symptoms
Cyanide	Hydroxocobalamin 70 mg/kg (max 5 g) or sodium nitrate; 0.33mL/kg *iv* (max 10 mL) followed by sodium thiosulfate (25%) 1.65 mL/kg *iv* (max 50 mL)	Hydroxocobalamin may be repeated × 1 if needed

two[5]. Clinical findings in bTBI have a similar spectrum to injuries seen in the typical practice of critical care physicians and include edema, contusion, diffuse axonal injury, hematomas, and hemorrhage[5]. A study by Ling *et al*[19] based on the conflicts in Iraq in Afghanistan suggest that the pathophysiology in bTBI may be different with increased vasospasm and pseudoaneurysms as well as onset of cerebral edema much earlier in the course of bTBI than other TBI. Additionally they demonstrated early decompressive craniectomy in these patients may reduce mortality. With the exception of early craniectomy, current treatment strategies for bTBI do not differ from more common severe closed head injury[5]. Specific pediatric considerations include age appropriate equipment, assessment tools such as the pediatric Glasgow Coma Score, and recognition of the specific vulnerabilities of children to bTBI (Table 1).

Ophthalmologic and auditory blast injury

Significant ophthalmologic injury may occur in up to 10% of blast victims and may include a perforated globe, foreign body, air embolism, fractures, or globe rupture from the over pressure wave[13]. Auditory injury is also common in blast injury occurring in 9%-47% of victims[7]. While both ophthalmologic and auditory injuries are common and may require follow-up (such as globe rupture within 12 h) they should be addressed after life threatening injuries.

CHEMICAL AGENTS

There are estimated to be over 50 chemical agents that can be used as weapons, many of which have a high probability of injury. Children may often be the index case in the event of a chemical agent attack due to their inherent vulnerabilities (Table 1). Exposure to chemical agents is usually *via* either the respiratory system or skin with direct and systemic toxicity possible in either route.

Skin decontamination of suspected victims is imperative as it limits further absorption by the patient as well as preventing healthcare worker exposure. Decontamination ("The solution to pollution is dilution") is best done with 0.5% hypochlorite solutions or large amounts of soap and water after removal of all clothing and jewelry. Decontamination should be done by personnel in appropriate personal protective equipment[20]. Following this, the patient should be blotted dry instead of scrubbed dry as this can lead to increased cutaneous absorption through abrasions in the skin. Isolation is not required after thorough decontamination[21].

Nerve agents [Tabun (GA), Sarin (GB), Soman (GD), and VX]

Nerve agents can be absorbed, ingested, and inhaled (if in aerosolized form). Nerve agents are colorless liquids at room temperature and generally odorless and tasteless. Although they range in severity (VX is the most potent), all are organophosphate analogs and inhibitors of the enzyme acetyl cholinesterase, resulting in excessive acetylcholine stimulation of both nicotinic and muscarinic receptors.

Signs and symptoms depend on the form of the agent, concentration, and environmental variables. Aerosolized agents produce symptoms within minutes while cutaneous exposure symptoms may not develop for hours. Initial symptoms are often best remembered by SLUDGE (salivation, lacrimation, urination, defecation, GI upset, and emesis). More severe symptoms consist of respiratory (cough, wheezing with bronchorrhea, dyspnea, respiratory depression and cyanosis), cardiovascular (bradycardia, hypotension, and atrioventricular block), and central nervous system (muscle fasciculations, seizures, ataxia, and altered mental status including coma). It is important to note that children may not exhibit miosis to the same degree as adults but do exhibit a high incidence of weakness/hypotonia. Pediatric patients are at higher risk for severe toxicity than adults (Table 1).

The diagnosis of nerve agent exposure is generally made using presenting symptoms and response to antidotes. Although red blood cell or plasma acetyl cholinesterase levels can be measured, this test is not widely available on a rapid basis. In addition, nerve agent detection devices are available in certain settings (generally military and homeland defense) but not generally found in civilian healthcare settings. Decontamination (outlined above) is key to both treatment and prevention of contamination of providers.

Death, usually as a result of respiratory failure, can occur within 5-10 min of lethal dose exposure without proper treatment. Treatment consists of antidotes for both muscarinic (atropine) and nicotinic (pralidoxime chloride) with pediatric dosing provided in Table 2[22]. Atropine is indicated for all patients exhibiting signs/symptoms of nerve agent poisoning. Atropine should be

Table 3 Guidelines for the use of Mark I kits in pediatric patients

Pediatric patients	Mark I kits
3-7 yr (approximately 13-25 kg)	One Mark I kit as maximum dose
8-14 yr (approximately 26-50 kg)	Two Mark I kits as maximum dose
> 14 yr (approximately > 51 kg)	Three Mark I kits as maximum dose

Mark I kit: 2 mg atropine and 600 mg 2-PAM; PAM: Pralidoxime.

repeated every 2-5 min if symptoms persist[22]. Both pediatric intramuscular atropine (0.25, 0.5, 1 mg dosages) and adult (2 mg) auto injectors are available although pediatric ones may be less available in some settings. Patients with severe sign/symptoms should also be given pralidoxime chloride (2-PAM) and a benzodiazepine. 2-PAM is used to treat the nicotinic receptor blockage by binding to the nerve agent, thus "re-activating" the acetylcholinesterase which can now break down the excessive acetylcholine present, provided enzyme "aging" or inactivation has not occurred. Currently there are only adult auto injectors (600 mg of 2-PAM) which together with the 2 mg atropine adult autoinjectors (Mark- I kit) can be used in pediatric patients when necessary. The Pediatric Expert Advisory Panel of Columbia University's Program for Pediatric Preparedness at the National Center for Disaster Preparedness has published guidelines on the use of Mark I kits in pediatric patients (Table 3). There are newer types of kits that combine the two agents in to one syringe for easier administration. Benzodiazepines (with midazolam as the preferred treatment) are given concurrently with 2-PAM to both prevent as well as treat seizures.

Vesicants

Sulfur Mustard is a vesicant that forms blisters upon skin contact and has been used on occasion since World War I including against the Kurdish population in Iraq. Although other vesicants exist such as Lewisite, they are considered to be of less risk for weaponization[4]. Vesicants are alkylating agents that cause damage to rapidly reproducing cells. Although vesicants cause less morbidity than nerve agents, they can cause significant long-term morbidity with extensive damage to skin, respiratory system, eyes, as well as bone marrow suppression. Mortality is usually from respiratory failure. Pediatric patients again exhibit a greater vulnerability to these agents due to faster skin absorption and proximity to agents settling near the ground (Table 1). If ingested, vesicants can also cause extensive intestinal mucosal injury. Although extensive clinical symptoms may not present until hours after exposure, skin damage can occur within minutes unless prompt decontamination is done. In general care =is supportive (similar to traditional burn care except for not requiring high volume fluid administration as in traditional burns) except in the case of lewisite for which British Anti-Lewisite can be used (3 mg/kg *im* q 4-6 h)[20].

Pulmonary agents

Chlorine and phosgene are the classic pulmonary agents but there are other pulmonary agents that can cause significant injury such as methyl isocyanate which was accidentally released in Bhopal, India in 1984 causing over 3000 deaths. Pulmonary agents have an odor of newly cut hay or grass and symptoms start with eye and skin irritation[21]. Significant respiratory symptoms can be delayed up to 24 h[23]. Symptoms include airway irritation (coughing, wheezing) with subsequent pulmonary edema and respiratory failure. Injury can occur to both Type I and Ⅱ pneumocytes as well as alveolar macrophages with later release of prostaglandins and bradykinin producing vasodilatation and increased capillary permeability[23]. See Table 1 for pediatric specific vulnerabilities. Decontamination (moving to fresh air and supplying oxygen) is key to the management of these patients. Treatment for respiratory failure is similar to other causes of respiratory failure. Adjunct treatments that have been used but lack definitive recommendations include corticosteroids as well as in the case of phosgene, N-acetylcholine.

Cyanide

Cyanide is a potent toxin that disrupts cellular metabolism by inhibiting cytochrome oxidase with interruption of oxidative phosphorylation. Cyanide intoxication can be caused by inhalation, ingestion or transdermal absorption of vapor, solid, and liquid forms. Fortunately cyanide is difficult to formulate into a chemical weapon due to it being highly volatile and chemically unstable. The classic presentation of cyanide poisoning is hypoxia without evidence of cyanosis. Mild symptoms include tachypnea, dizziness, nausea, vomiting, and headaches. Significant exposure can cause seizures, coma, respiratory arrest, and cardiac arrest within minutes.

Cyanide poisoning should be suspected in patients with a sudden change in mental status and significant metabolic acidosis. Characteristically patients have a bitter almond odor with a cherry red appearance of the skin. Laboratory testing will reveal elevated serum lactate levels, a narrow arterial-venous oxygen saturation difference, and elevated blood cyanide levels.

Decontamination (soap and water) should be performed in the event of cutaneous exposure. Mild systemic symptoms generally resolve with fresh air. Severe symptoms (coma, respiratory distress, *etc.*) are an indication for administration of an antidote in addition to critical care support as indicated. Hydroxocobalamin is now recommended as first line treatment due to its improved safety profile as compared to traditional cyanide antidote kits (Table 2). Hydroxocobalamin's mechanism of action is binding with cyanide to form cyanocobalamin which is excreted renally[24]. Traditional cyanide antidote kits consist of sodium nitrite and sodium thiosulfate. A third component, amyl nitrite is no longer recommended due to questionable efficacy. Nitrite administration is now used as a second line treatment due to concerns of overproduction of methemoglobin which may compromise oxygen-carrying capacity, especially in young children, as well as hypotension that can be seen with nitrite infusions.

Riot control agents

Riot control agents are also known as lacrimators, "tear gas", and pepper spray. The most commonly used riot control agents are CS and CN. Although these agents produce mostly irritant symptoms to the eye they can be fatal as seen with a terrorist attack in Russia in 2002 where over 100 were killed. These agents are also alkylating but do not produce tissue damage similar to vesicants. In general they cause pain, conjunctival injection, blepharospasm, and lacrimation. In some cases respiratory symptoms may occur (laryngospasm and bronchospasm) and is the cause of fatalities. Treatment consists of eye and skin irrigation as well as supportive respiratory care, including bronchodilators, if needed.

BIOLOGIC AGENTS

The use of biologic weapons has been and continues to be a great threat to our population. The ability to recognize that an attack has occurred and the ability to differentiate this from a natural outbreak can be difficult as symptoms of these agents may be delayed days to weeks after the attack. It is imperative that physicians recognize patterns that could indicate the early manifestations of a bioterrorist attack. A sudden outbreak of an unusual illness or the diagnosis of a rare disease is likely to be the first indication. Epidemiologic surveillance systems have been set up for early detection with the goals of early institution of preventative measures such as vaccination, isolation, prophylaxis, and institution of other treatment modalities[25]. Children, like in previous sections, have particular vulnerabilities to biological attacks (Table 1).

The Soviet Union, United States, and Japan all developed biological weapons programs in the 20th century. It is suspected that Japanese planes dropped fleas carrying plague over China during World War Ⅱ. The Convention of the Prohibition of the Development, Production, and Stockpiling of Bacteriologic and Toxin Weapons was held in 1972, with over 140 countries signing[25]. Despite the signing of this document, the threat of biological warfare continues with the rise in terrorist groups. The release of anthrax spores through the United States postal system and the release of anthrax into the population following the September 11, 2011 terrorist attacks demonstrate that this is a continued threat. The United States continues to develop aggressive measure of surveillance and protection[26].

The Center for Disease Control (CDC) has categorized agents into three groups based on morbidity and mortality if used as a biological weapon. Category A agents pose the greatest risk due to their easy dissemination, high mortality rates, and require special action for public health preparedness. Category B agents are moderately easy to disseminate, result in high morbidity and low mortality and require enhancement of the CDC's surveillance. Category C agents include emerging pathogens that are engineered for mass dissemination in the future[27]. We will address the category A agents.

Anthrax

Anthrax is caused by a gram-negative, spore forming bacteria, *Bacillus anthracis* (*B anthracis*). It is naturally occurring in animals as they ingest spores from the soil Anthrax occurs in humans in 3 different forms: GI, cutaneous, and inhalational anthrax. Cutaneous and GI anthrax both occur naturally and are transmitted through breaks in the skin or ingestion of infected meat respectively. Inhalational anthrax rarely occurs naturally with no cases reported in the United States since 1978. Inhalational anthrax is thought to hold the most threat as it is expected to account for the most morbidity and mortality. Anthrax secretes two exotoxins, edema toxin and lethal toxin. These result in massive edema and a cytokine storm[28].

Papules form in cutaneous anthrax in 1-7 d following exposure. These papules then become vesicles that ulcerate and form a black eschar. Symptoms of inhalational anthrax typically occur 1-7 d after exposure but can occur as late as 60 d after exposure. Early symptoms are subtle, resembling a nonspecific upper respiratory infection. Later the child will develop a high fever, shock, and death. Autopsy studies of patients with inhalational anthrax show hemorrhagic thoracic lymphadenitis and mediastinitis with very few exhibiting signs of pneumonia. Up to 50% of patients will also develop meningitis[28,29].

Because diagnostic tests including enzyme-linked immunosorbent assay and polymerase chain reaction are only available at the national reference laboratories diagnosis of an outbreak could be delayed. Diagnosis on routine blood culture could be missed if the laboratory is not alerted to *B anthracis* being a possible cause. Antimicrobial treatment is outlined in Table 4. No widespread vaccine distribution is currently available, and person to person transmission has not been reported[29].

Plague

Yersinia pestis is a gram-negative bacillus, sometimes coccobacillus, known to cause plague. It occurs naturally in the forms of septicemia, bubonic and pneumonic forms. Pneumonic plague is the most likely to be seen in a bioterrorism as aerosolized forms would be easily disseminated. Pneumonic plague results in a multilobar, hemorrhagic and necrotizing bronchopneumonia. Unlike naturally occurring plague, plague following a biological attack will present with respiratory symptoms without the development of the buboes. Patients would likely develop fever and cough within 6 d of exposure and rapidly progress to severe bronchopneumonia. Untreated pneumonic plague has resulted in nearly 100% mortality[29]. An additional clue of intentional dissemination would be cases presenting in areas not known to have animal infection[30].

Large numbers of previously healthy patients presenting with severe pneumonia, hemoptysis, and sepsis would be the first signs of a biological attack with plague. There are no rapid tests available to detect *Y pestis*. A gram stain of blood or sputum may reveal a gram-negative bacilli 24-48 h after inoculation. Table 4 outlines a variety of treatment regimens available[29].

Table 4 Management of biologic agents

Agent	Pediatric dosing	Notes
Inhalational anthrax	Ciprofloxacin 10-15 mg/kg *iv* q 12 h (max 400 mg) or doxycycline 2.2 mg/kg *iv* q 12 h (max 100 mg) plus clindamycin 10-15 mg/kg q 8 plus penicillin G 400-600 k U/kg per day *iv* divided q 4 h prophylaxis for exposed contacts ciprofloxacin 15 mg/kg *po* q 12 h or doxycycline 2.2 mg/kg *po* q 12 h	Switch to oral therapy when patient shows signs of improvement At least one agent should have good CNS penetration Prophylaxis is for a 60 d course Amoxicillin or levofloxacin are second line
Plague	Gentamycin 2.5 mg/kg *iv* q 8 h or streptomycin 15 mg/kg *im* q 12 h (max 2 mg/d) or doxycycline 2.2 mg/kg *iv* q 12 h (max 200 mg/d) or ciprofloxacin 15 mg/kg *iv* q 12 h prophylaxis for exposed contacts trimethoprim/sulfa 4 mg/kg *po* q 12 h	Chloramphenical or Levofloxacin can also be used Prophylaxis should be continued for 5-7 d
Tularemia	Same as therapy for plague	
Botulism	Infants < 1 yr human-derived botulinum immunoglobulin children > 1 yr equine serum botulism antitoxin	In United States call 1-800-222-1222 or 770-488-7100 Outside United States contact local health agencies

CNS: Central nervous system.

Small pox

Any case of small pox, variola major, that is identified would be considered an act of terrorism. Small pox has been eradicated and no child has been routinely vaccinated against small pox since 1971. Small pox is highly contagious, with only a few viral molecules needed to induce disease. It is believed that the only remaining samples of this virus are kept secure at the CDC and in Russia, although there are some who believe other countries may have samples of it in their possession[29].

The incubation period of small pox is from 7-19 d after exposure. Initially symptoms are relatively nonspecific with fever, malaise, vomiting, headache and backache. Two to three days later the patient develops an erythematous macular rash that progresses to papules and then pustules, which spread centrifugally. Death occurs in the second week of illness with multi-organ failure due to overwhelming viremia.

Diagnosis of small pox will be clinical as there are no widely available assays. Initial suspicion should be reported immediately to the health department. Patients exposed to a case will need to be monitored for a minimum of 17 d on airborne and contact precautions in the hospital or isolated in their homes. They should remain isolated until they are ruled out (PCR assays are available at national laboratories) or when the vesicles have lost their scab. Vaccines obtained in the last 3 years are thought to provide full immunity. Treatment is supportive care. There are no FDA approved anti-virals although cidofovir has been shown useful in animal models. Vaccination 72-96 h after exposure provides good protection against developing disease and also decreases severity[25]. All close contacts will require vaccination and isolation.

Tularemia

Tularemia is caused by Francisella tularensis, a small, aerobic, gram-negative coccobacillus with extremely high virulence. It occurs naturally in the environment throughout North America and Europe. Humans are infected by insect bites, handling infected animal meat, or ingestion of contaminated water or food. An act of bioterrorism with tularemia would likely be in an aerosolized form, allowing for many to become ill with a single release[31].

In the event of an aerosolized tularemia attack, there would be an abrupt onset of patients presenting with flu-like symptoms and bronchitis 3-5 d post exposure. A large amount of those infected would present with severe cases of necrotizing hemorrhagic pneumonia, with or without bacteremia.

It is unlikely for tularemia to be identified with routine culture techniques. Rapid tests are primarily only run at research and reference laboratories. Serum antibody titers can be diagnostic but take 10 d to become positive. Standard precautions are all that is required as tularemia is not spread person to person. Patients have a significantly improved course with early initiation of the appropriate antibiotics (Table 4) and prophylaxis should be provided to others exposed to the attack[31].

Botulism

Botulinum toxin is produced by Clostridium botulinum, an anaerobic bacteria, and is the most lethal toxin known. Botulism can be spread naturally by three mechanisms: infantile botulism, wound botulism, and intestinal botulism. Botulinum toxin causes the inhibition of the release of acetylcholine at the nervous-skeletal muscle junction, thus producing a paralysis. Patients primarily die due to respiratory failure. Even with supportive care, recovery can take weeks to months as new axons must grow on each neuron[29].

In the event of a bioterrorism attack, the particles would likely be released and inhaled[32]. Symptoms can present within 12-24 h after exposure, with cranial nerve palsies presenting first, followed by descending paralysis progressing to respiratory failure. Clinical symptoms are constipation, ileus, dry mouth and mydriasis. The "gold standard" for diagnosis is a bioassay but treatment should not be delayed pending these results. Supportive care and ventilator support is the most important aspect of treatment. Antitoxin is available in two forms, bivalent human

Table 5 Viral hemorrhagic fever, virus and disease

Family	Virus	Disease
Arenaviruses	Lassa virus	Lassa fever
	Junin	Argentine hemorrhagic fever
	Machupo	Bolivian hemorrhagic fever
Bunyaviruses	CCHF	Cremiean-Congo hemorrhagic fever
	RVF	Rift Valley fever
	Hantavirus	Hemorrhagic fever with renal syndrome
Filoviruses	Ebola virus	Ebola hemorrhagic fever
	Marburg virus	Marburg hemorrhagic fever
Flavivirus	Yellow fever virus	Yellow fever
	KFD virus	KFD
	OHF virus	Omsk hemorrhagic fever
	DENV 1-4 viruses	Dengue hemorrhagic fever
Rhabdovirus	Bas-Congo virus	Bas-Congo hemorrhagic fever

CCHF: Crimean congo hemorrhagic fever; RVF: Rift valley fever; KFD: Kyasanur forest disease; OHF: Omsk hemorrhagic fever; DENV: Dengue hemorrhagic fever virus.

antiserum and equine heptavalent antitoxin, and should be administered at the first onset of symptoms. This will unlikely be available in massive quantities during a mass attack and will only shorten the course of illness. Prophylactic vaccination is reserved for at risk individuals, primarily laboratory workers[25].

Viral hemorrhagic fevers

The viral hemorrhagic fevers are produced by a variety of viruses originating from one of five virus families (Table 5). They are grouped by their ability to produce fever, shock, and bleeding. They are all spread by aerosolized particles, excluding dengue fever, which is blood-borne, and produce an illness with high morbidity and mortality.

All of the viral hemorrhagic fevers present with a nonspecific febrile illness including headache, myalgia and malaise. As they progress, the patient develops shock and hemorrhage. The cause of hemorrhage can vary depending on the causative agent. Most are multi-factorial in nature. Diagnosis should begin with a careful travel history to possible endemic areas as well as exposure to animals or animal feces. Patients have detectable viremia with most viruses identified through rapid enzyme immunoassays[25].

Supportive care is the mainstay for the hemorrhagic fevers. Vigorous fluid resuscitation and control of hemorrhage with platelets, red blood cells, and clotting factors will often require intensive care. Ribavirin is indicated only in Lassa fever but has been used experimentally in a few of the other viruses[29].

CONCLUSION

Terrorist incidents continue to occur and it is imperative that the critical care provider be familiar with signs, symptoms, and basic treatment of the injuries and illnesses caused by potential terrorist modalities. While these events are thankfully rare, the prompt recognition of a possible chemical or biological attack is crucial to limiting the damage caused by such an attack by instituting appropriate decontamination, treatment, and preventative measures. Familiarity with injuries specific to a blast should prepare the provider to anticipate and intervene appropriately when caring for these patients. For further information please refer to the agency for healthcare research and quality website at http://archive.ahrq.gov/research/pedprep/index.html.

REFERENCES

1 **National Commission on Children and Disasters**. 2010 report to the President and Congress. Available from: URL: http://archive.ahrq.gov/prep/nccdreport/index.htm
2 **Matos RI**, Holcomb JB, Callahan C, Spinella PC. Increased mortality rates of young children with traumatic injuries at a US army combat support hospital in Baghdad, Iraq, 2004. *Pediatrics* 2008; **122**: e959-e966 [PMID: 18977963 DOI: 10.1542/peds.2008-1244]
3 **Agency for Healthcare Research and Quality**. Blast Terrorism. Available from: URL: http://archive.ahrq.gov/research/pedprep/pedchap7.htm
4 **Defense USAMRICD**. Field Management of Chemical Casualties. Chemical Casualty Care Division USAMRICD.Aberdeen Proving Ground. Frederick, MD, 2007
5 **Hicks RR**, Fertig SJ, Desrocher RE, Koroshetz WJ, Pancrazio JJ. Neurological effects of blast injury. *J Trauma* 2010; **68**: 1257-1263 [PMID: 20453776 DOI: 10.1097/TA.0b013e3181d8956d]
6 **Champion HR**, Holcomb JB, Young LA. Injuries from explosions: physics, biophysics, pathology, and required research focus. *J Trauma* 2009; **66**: 1468-1477; discussion 1477 [PMID: 19430256 DOI: 10.1097/TA.0b013e3181a27e7f]
7 **Ritenour AE**, Baskin TW. Primary blast injury: update on diagnosis and treatment. *Crit Care Med* 2008; **36**: S311-S317 [PMID: 18594258 DOI: 10.1097/CCM.0b013e31817e2a8c]
8 **Gutierrez de Ceballos JP**, Turégano Fuentes F, Perez Diaz D, Sanz Sanchez M, Martin Llorente C, Guerrero Sanz JE. Casualties treated at the closest hospital in the Madrid, March 11, terrorist bombings. *Crit Care Med* 2005; **33**: S107-S112 [PMID: 15640672 DOI: 10.1097/01.CCM.0000151072.17826.72]
9 **Leibovici D**, Gofrit ON, Stein M, Shapira SC, Noga Y, Heruti RJ, Shemer J. Blast injuries: bus versus open-air bombings--a comparative study of injuries in survivors of open-air versus confined-space explosions. *J Trauma* 1996; **41**: 1030-1035 [PMID: 8970558 DOI: 10.1097/00005373-199612000-00015]
10 **Mellor SG**, Cooper GJ. Analysis of 828 servicemen killed or injured by explosion in Northern Ireland 1970-84: the Hostile Action Casualty System. *Br J Surg* 1989; **76**: 1006-1010 [PMID: 2597940 DOI: 10.1002/bjs.1800761006]
11 **Tsokos M**, Paulsen F, Petri S, Madea B, Puschel K, Turk EE. Histologic, immunohistochemical, and ultrastructural findings in human blast lung injury. *Am J Respir Crit Care Med* 2003; **168**: 549-555 [PMID: 12842857 DOI: 10.1164/rccm.200304-528OC]
12 **Avidan V**, Hersch M, Armon Y, Spira R, Aharoni D, Reissman P, Schecter WP. Blast lung injury: clinical manifestations, treatment, and outcome. *Am J Surg* 2005; **190**: 927-931 [PMID: 16307948 DOI: 10.1016/j.amjsurg.2005.08.022]
13 **Centers for Disease Control and Prevention**. Explosion and blast injuries: A primer for clinicians. Last accessed 2013. Available from: URL: http://www.cdc.gov/masstrauma/preparedness/primer.pdf
14 **Sorkine P**, Szold O, Kluger Y, Halpern P, Weinbroum AA, Fleishon R, Silbiger A, Rudick V. Permissive hypercapnia ventilation in patients with severe pulmonary blast injury. *J Trauma* 1998; **45**: 35-38 [PMID: 9680008 DOI: 10.1097/00005373-199807000-00006]
15 **Argyros GJ**. Management of primary blast injury. *Toxicol-*

ogy 1997; **121**: 105-115 [PMID: 9217319 DOI: 10.1016/S0300-483X(97)03659-7]
16 **Irwin RJ**, Lerner MR, Bealer JF, Brackett DJ, Tuggle DW. Cardiopulmonary physiology of primary blast injury. *J Trauma* 1997; **43**: 650-655 [PMID: 9356063 DOI: 10.1097/00005373-199710000-00015]
17 **Irwin RJ**, Lerner MR, Bealer JF, Mantor PC, Brackett DJ, Tuggle DW. Shock after blast wave injury is caused by a vagally mediated reflex. *J Trauma* 1999; **47**: 105-110 [PMID: 10421195 DOI: 10.1097/00005373-199907000-00023]
18 **Owers C**, Morgan JL, Garner JP. Abdominal trauma in primary blast injury. *Br J Surg* 2011; **98**: 168-179 [PMID: 21104699 DOI: 10.1002/bjs.7268]
19 **Ling G**, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. *J Neurotrauma* 2009; **26**: 815-825 [PMID: 19397423 DOI: 10.1089/neu.2007.0484]
20 **Heon D**, Foltin GL. Pediatric Emergency Preparedness for Natural Disasters, Terrorism, and Public Health Emergencies-National Consensus Conference. *Clin Pediatr Emerg Med* 2009; **10**: 186-194 [DOI: 10.1016/j.cpem.2009.06.006]
21 **Defense USAMRICD**. In: Field Management of Chemical Casualties. 2nd edn. Aberdeen Proving Ground, MD: Chemical Casualty Care Division USAMRICD; 2000: 96-135.
22 **Garrett AL**, Readlener IE. Pediatric Emergency Preparedness for Natural Disasters, Terrorism, and Public Health Emergencies: A National Consensus Conference: 2009 Update. Available from: URL: http://academiccommons.columbia.edu/catalog/ac:126143
23 **Baker DJ**. Critical care requirements after mass toxic agent release. *Crit Care Med* 2005; **33**: S66-S74 [PMID: 15640682 DOI: 10.1097/01.CCM.0000151069.06678.A5]
24 **Henretig FM**. Preparation for Terrorist Threats: Biologic and Chemical Agents. *Clin Pediatr Emerg Med* 2009; **10**: 130-135 [DOI: 10.1016/j.cpem.2009.07.006]
25 **Diseases UAMRIID**. Medical Management of Biological Casualties Handbook. 7th edn. Fort Detrick, Frederick, MD, 2001
26 **Michael W S**, Julia A M. Chemical-biological terrorism and its impact on children. *Pediatrics* 2006; **118**: 1267-1278 [PMID: 16951026 DOI: 10.1542/peds.2006-1700]
27 **Centers for Disease Control and Prevention**. Bioterrorism Agents/Diseases by Category. Available from: URL: http://www.bt.cdc.gov/agent/agentlist-category.asp
28 **Inglesby TV**, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Hauer J, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 1999; **281**: 1735-1745 [PMID: 10328075]
29 **Pilip L**. Graham III GLF, F. Meridith Sonnett. Terrorism and Mass Casualty Events. Edited by Nichols DG, Fourth edn. In: Rogers's Textbook of Pediatric Intensive Care. Philidelphia, PA: Lippincott Williams and Wilkins; 2008: 427-440
30 **Inglesby TV**, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Koerner JF, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Schoch-Spana M, Tonat K. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 2000; **283**: 2281-2290 [PMID: 10807389 DOI: 10.1001/jama.283.17.2281]
31 **Dennis DT**, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Layton M, Lillibridge SR, McDade JE, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Tularemia as a biological weapon: medical and public health management. *JAMA* 2001; **285**: 2763-2773 [PMID: 11386933 DOI: 10.1001/jama.285.21.2763]
32 **Cieslak TJ**, Henretig FM. Ring-a-ring-a-roses: bioterrorism and its peculiar relevance to pediatrics. *Curr Opin Pediatr* 2003; **15**: 107-111 [PMID: 12544281 DOI: 10.1097/00008480-200302000-00018]

P- Reviewers: Conti A, KlugerY, Moghazy A
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.24

World J Crit Care Med 2014 February 4; 3(1): 24-33
ISSN 2220-3141 (online)

Controversies in fluid therapy: Type, dose and toxicity

Robert C McDermid, Karthik Raghunathan, Adam Romanovsky, Andrew D Shaw, Sean M Bagshaw

Robert C McDermid, Adam Romanovsky, Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G2B7, Canada
Karthik Raghunathan, Andrew D Shaw, Department of Anesthesiology, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
Andrew D Shaw, Department of Critical Care Medicine, Duke University Medical Center/Durham VAMC, Durham, NC 90484, United States
Author contributions: All the authors contributed to drafting and critical revision of manuscript.
Supported by Canada Research Chair in Critical Care Nephrology; Clinical Investigator Award from Alberta Innovates-Health Solutions to Bagshaw MS
Correspondence to: Dr. Sean M Bagshaw, Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, 3C1.12 Walter C. Mackenzie Centre, 8440-122 ST NW, Edmonton, AB T6G2B7, Canada. bagshaw@ualberta.ca
Telephone: +1-780-4076755 Fax: +1-780-4071228
Received: June 7, 2013 Revised: October 30, 2013
Accepted: December 12, 2013
Published online: February 4, 2014

Abstract

Fluid therapy is perhaps the most common intervention received by acutely ill hospitalized patients; however, a number of critical questions on the efficacy and safety of the type and dose remain. In this review, recent insights derived from randomized trials in terms of fluid type, dose and toxicity are discussed. We contend that the prescription of fluid therapy is context-specific and that any fluid can be harmful if administered inappropriately. When contrasting "crystalloid *vs* colloid", differences in efficacy are modest but differences in safety are significant. Differences in chloride load and strong ion difference across solutions appear to be clinically important. Phases of fluid therapy in acutely ill patients are recognized, including acute resuscitation, maintaining homeostasis, and recovery phases. Quantitative toxicity (fluid overload) is associated with adverse outcomes and can be mitigated when fluid therapy based on functional hemodynamic parameters that predict volume responsiveness and minimization of non-essential fluid. Qualitative toxicity (fluid type), in particular for iatrogenic acute kidney injury and metabolic acidosis, remain a concern for synthetic colloids and isotonic saline, respectively. Physiologically balanced crystalloids may be the "default" fluid for acutely ill patients and the role for colloids, in particular hydroxyethyl starch, is increasingly unclear. We contend the prescription of fluid therapy is analogous to the prescription of any drug used in critically ill patients.

Key words: Fluid therapy; Resuscitation; Critical illness; Peri-operative; Toxicity; Saline; Crystalloid; Colloid

Core tip: Fluid therapy is exceedingly common in acutely ill patients; however, numerous questions on the efficacy and safety of fluid therapy in terms of the type and dose remain. Fluid therapy prescription is context-specific and any fluid type can be harmful if administered inappropriately. When considering crystalloids versus colloids, differences in efficacy are modest but the risk of kidney toxicity and bleeding complications with hydroxyethyl starch appear more significant. The differences in chloride load across crystalloid solutions appears to have physiologic and clinically important effects, in particular for contributing to hyperchloremic metabolic acidosis, kidney injury and greater utilization of renal replacement therapy associated with 0.9% saline. Fluid therapy should be viewed as analogous to the prescription of any drug in acutely ill patients.

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(1): 24-33 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/24.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.24

INTRODUCTION

Intravenous (*iv*) fluid therapy is one of the most common interventions administered to acutely hospitalized patients; however, a number of fundamental questions about its efficacy and safety remain.

The origins of the administration of *iv* fluids for acute resuscitation date back to the cholera epidemic of the early 19th century, when Dr. Thomas A Latta first administered a warmed *iv* solution of "two drachams of muriate, two scruples of carbonate of soda to sixty ounces of water" to combat the profound dehydration in six patients hospitalized at the Leith Infirmary in Scotland[1]. With this non-sterile hypotonic solution, he was able to spare a few moribund patients from refractory hypovolemic shock. Impressive volumes of fluid (over 12 liters in some cases) were required to restore hemodynamics, and as described resulted in "...an immediate return of the pulse, and improvement in the respiration… [and in] the appearance of the patient [were] the immediate effects". Yet, even in 1832, an editorial subsequently published in the *Lancet* commented that "...the mass of the profession is unable to decide; and thus, instead of any uniform mode of treatment, every town and village has its different system or systems..." and that "...a suitable clinical investigation is required to resolve between such conflicting authorities…"[2]. As such, after nearly two centuries of advancements in the modern medicine, this editorial seemed to be remarkably familiar in many respects to our current state of knowledge regarding the optimal prescription of fluid therapy for acutely ill patients.

Fluid used in acute resuscitation should be viewed in the same context as any other drug administered to patients. Their prescription is certainly analogous to how drugs are prescribed (Table 1). This is relevant when considering that the vast majority of hospitalized acutely ill patients, including children, will receive *iv* fluid therapy, usually as some combination of crystalloids, colloids and/or blood products.

However, data have supported the notion that the form of fluid therapy prescribed is largely dependent on where medical care is provided (*i.e.,* country, region, hospital, care unit) and on the specialty of the clinician (*i.e.,* surgical, medical, anesthesia, emergency)[3,4]. There is wide variation in clinical practice with respect to the type and dose of fluid prescribed[3]. This variation in practice has historically been derived from a general lack of clarity in the literature on the principles of optimal fluid prescription (*i.e.,* efficacy and safety)-the idea of prescribing fluid therapy for "the right patient, at the right time, and in the right context". In the last few years, a number of large high-quality randomized trials have reported on the efficacy and safety intravenous fluid therapy for acute resuscitation in the critically ill[4-6]. These data are beginning to provide clarity to long-standing debates regarding fluid type and dose, during and following acute resuscitation and to better inform clinical practice to improve patient outcomes[7]. In this review, we discuss recent relevant evidence related to the type and dose of fluid therapy used in the resuscitation of critically ill patients.

Table 1 Overview of the analogy of prescribing fluid therapy and prescribing a drug

Steps for prescribing a drug	Prescribing an oral hypoglycemic medication	Prescribing fluid therapy
Define the clinical problem	Diabetes mellitus	Hypovolemia or other fluid responsive state
Specify the therapeutic objective	Lower blood glucose	Restore absolute/ relative fluid deficit
Verify the suitability of the drug	Class of oral hypoglycemic agent	Crystalloid, colloid or blood product
Write a prescription to start the drug	Order written by MD, verified and dispensed by pharmacy	Order written by MD, verified by pharmacy, blood bank or RN, administered by RN
Monitor therapeutic response of the drug	Blood glucose or hemoglobin A1C, evidence of adverse effect/ toxicity	Monitor hemodynamic profile and end-organ perfusion, evidence of dose-response toxicity
Write an order to discontinue	Order written by MD, verified by pharmacy	Order written by MD, administered by RN

Adapted from Raghunathan *et al*[58].

DOSE OF FLUID THERAPY

As aforementioned, *iv* fluid therapy is one of the most common and certainly may be one of the most important initial interventions in the resuscitation of acute ill patients. A key concept for dosing fluid therapy in critically ill patients is to actively address ongoing losses coupled with constant reassessment of need for further hemodynamic support. The routine practice of providing "maintenance" or replacement of unmeasured fluid deficits such as "third space losses" for most patients is questionable and often contributes unnecessary fluid accumulation. The optimal target endpoints for fluid therapy during resuscitation remain controversial. Recent data suggest static metrics of resuscitation, such as thresholds in central venous pressure (CVP), as currently recommended by the Surviving Sepsis Campaign[8], may not accurately correlate with restoration of intravascular volume and improvement in tissue oxygen delivery and may be associated with worse outcome[9]. Additional measures such as achieving a normalized central venous oxygen saturation (> 65%-70%) and rapid serum lactate clearance (> 20% in 2 h) in response to fluid resuscitation (± additional hemodynamic support) have been recommended and correlate with improve outcome, both of these endpoints also have important caveats to consider[9,10]. Rather, functional hemodynamic measures such as stroke volume variation, pulse pressure variation[11], bedside ultrasonic interrogation of cardiac output or respiratory variation in inferior vena cava diameter and additional novel dynamic metrics such changes in cardiac output associated with passive leg raising, changes in end-tidal CO_2 and end-expiratory endotracheal tube occlusion can better predict the hemodynamic response to fluid loading[12-15]. These

dynamic measures are superior to blood pressure, CVP, and urine output targets. Importantly, critically ill patients are heterogeneous and may vary considerably with respect to baseline susceptibilities, admission diagnoses and response to fluid loading. When conventional blood pressure or urine output targets are used to guide fluid loading in critically ill patients, often large doses of fluids are administered, and in these circumstances, colloids such as hydroxyethyl starch (HES) are associated with toxicity[7]. The use of fluid boluses in critically ill patients without integrating functional hemodynamic parameters may be associated with cardiovascular decompensation and worse outcome[5]. These observations would strongly support the need for individualized resuscitation goals that integrate functional hemodynamic measures rather than use of generic resuscitation endpoints.

TYPE OF FLUID THERAPY

For a given dose of fluid administered, toxicity may depend on the type and composition of fluid being administered and on patient susceptibilities and physiology. Both patient-specific and context-specific differences should be considered when selecting the type of fluid therapy to be administered.

The debate regarding the relative risks and benefits of colloid and crystalloid solutions has raged on for years. Although various forms of crystalloid solutions have been used in humans since the 1830s, it was approximately 100 years more before the technology to isolate albumin from serum was available. In World War Ⅱ, fractionated bovine albumin was first used on the battlefield as a resuscitation fluid. Synthetic colloids such as HES and gelatins have until recently been considered reasonable alternatives to albumin, due to their theoretical advantages such as mitigating the infectious risks of human blood products, improving blood rheology and microvascular flow, and modulating neutrophil aggregation. The choice of fluid type; however, has largely been a matter of individual clinician preference rather than being specifically directed by high-quality data from clinical trials.

In 1998, the crystalloid/colloid controversy came to a head with the publication of a systematic review that suggested that the use of human albumin was associated with one additional death for every 17 patients treated[16]. Despite this review having methodological misgivings, a political firestorm ensued when the Cochrane Injuries Group urged politicians to "take action" six weeks before the article was published by the *BMJ*. Unfortunately, the lay media reported the findings prior to peer review and publication, resulting in statistically-questionable, poorly-supported inflammatory news headlines such as "300 die as health chiefs dither"[17]. The director of the United Kingdom Cochrane Center went so far as to suggest that he would sue any doctor who gave him an infusion of albumin[15,16].

Due to this ongoing narrative, interest in the patterns of clinical use of crystalloid and colloid solutions for fluid resuscitation in the intensive care unit (ICU) has increased. An international study of 391 ICUs across 25 countries observed that colloid therapy was the primary fluid used in 48% of instances for acute resuscitation, whereas crystalloid and blood products were used in 33% and 28% of instances, respectively[3]. However, the variation in the type of fluid administered was six-fold different between countries. These data suggested that local factors, such as "unit protocols" and commercial marketing played an important role in guiding clinicians' choice of fluid type for resuscitation. These data also recommended better evidence in the form of high-quality randomized trials were needed along with appropriate mechanisms to translate new knowledge from such data into bedside practice.

Several studies have repeated provided a physiological rationale for the preferential use of a colloid (with an emphasis on HES) over crystalloid therapy for resuscitation in septic shock and other in states of acute stress such as peri-operatively. HES solutions have been shown to attenuate the acute inflammatory response[18-21], mitigate endothelial barrier dysfunction and vascular leak[18,22], and preserve intestinal barrier function[17]. Small clinical trials have suggested superiority of HES solutions for resuscitation of the microcirculation in sepsis[22]. Small randomized clinical trials have also shown that early fluid resuscitation with HES solutions results in more rapid hemodynamic stabilization and shock reversal (*i.e.,* greater efficacy) compared with crystalloids, and require significantly less fluid to restore intravascular volume[23,24].

Several more recent randomized trials have specifically evaluated the "colloid/crystalloid" hypothesis for fluid resuscitation in critically ill patients. The SAFE[25] (4% albumin in 0.9% saline *vs* 0.9% saline), CHEST[6] (6% HES in 0.9% saline *vs* 0.9% saline) and 6S[7] (6% HES in Ringer's acetate *vs* Ringer's acetate) trials were specifically designed to evaluate the effectiveness of colloids against corresponding crystalloids. These trials have shown that the efficacy of volume expansion of colloids over crystalloids (*i.e.,* the ability to increase plasma volume) is greater for colloids (ratio 1.2-1.4:1 for crystalloid:colloid about 20%-40% enhanced effect with colloids); however, less than conventional teaching and evidence generated in experimental models[5-7,25]. This may be accounted for by the collapse of the classical "Starling model" based understanding of fluid movement across capillary membranes in critically ill states, where vascular endothelia is disrupted and hydrostatic (*i.e.,* systemic venous hypertension/endothelial injury) and oncotic (*i.e.,* hypoproteinemia) forces are deranged. Moreover, this also highlights that these issues are dynamic during the coarse of critical illness and that variable fluid types are expected to have heterogeneous effects that will depend upon: (1) the relative chloride load (*i.e.,* strong ion difference); (2) the presence of colloid (*i.e.,* HES or albumin); and (3) the underlying/evolving severity in patients pathophysiology.

The ideal electrolyte solution is yet undiscovered; however, for resuscitation may be one that reasonably parallels the plasma (chloride) and has a strong ion difference that is greater than zero (0.9% saline) but less

Table 2 Summary of studies comparing isotonic saline to balanced crystalloid solutions

Study	Design	Population	Solutions	Outcome
McFarlane *et al*[59]	RCT	Elective hepatobiliary/ pancreatic surgery	0.9% saline *vs* PL-148	Iatrogenic metabolic acidosis with 0.9% saline
Wilkes *et al*[47]	RCT	Major abdominal surgery	0.9% saline *vs* Hartmann's (in HES)	Iatrogenic metabolic acidosis with 0.9% saline
O'Malley *et al*[48]	RCT	Kidney transplant recipients	0.9% saline *vs* RL	Iatrogenic metabolic acidosis and hyperkalemia with 0.9% saline
Yunos *et al*[56]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	More acidosis with chloride-rich; more alkalosis and reduced cost with chloride-poor
Chowdbury *et al*[26]	RCT (cross-over)	Healthy volunteers	0.9% saline *vs* PL-148 (2 L infusion)	↑ Δ [Cl⁻]; ↑ Strong ion difference; ↓ RBF; ↑ weight gain; ↑ extravascular volume; ↑ time to micturation
Chua *et al*[49]	Retrospective	Critically ill with DKA	0.9% saline *vs* PL-148	More rapid resolution of acidosis with PL-148
Shaw *et al*[55]	Retrospective	Major abdominal surgery	0.9% saline *vs* PL-148	↑ Major infection; ↑ composite of complications; ↑ blood transfusions; and ↑ RRT with 0.9% saline
Yunos *et al*[57]	Prospective before-and-after	Critically ill patients	Chloride-rich *vs* chloride-poor fluid strategy	↑ AKI (KDIGO stage Ⅱ / Ⅲ); ↑ RRT with chloride-rich strategy

Adapted from Raghunathan *et al*[58]. RCT: Randomized clinical trial; 0.9% saline: Normal saline; PL: Plasmalyte; RL: Ringers lactate; RBF: Renal blood flow; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; HES: Hydroxyethyl starch; RRT: Renal replacement therapy; KDIGO: Kidney disease improving global outcomes; FO: Fluid overload; FB: Fluid balance.

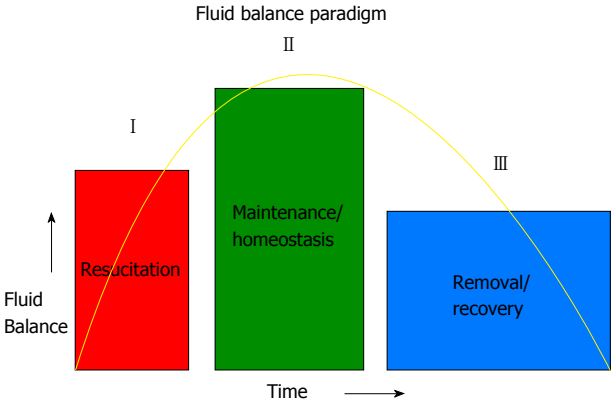


Figure 1 Fluid balance paradigm. The management of fluid therapy in critical illness can be conceptually viewed across three broad phases differentiated according to clinical status of the patient. During the "resuscitation" phase, the goal is restoration of effective intra-vascular volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected. During the maintenance phase, the goal is maintenance of intravascular volume homeostasis. The broad aim here would be to mitigate excessive fluid accumulation and prevent unnecessary fluid loading. During the recovery phase, passive and/or active fluid removal would correspond to organ recovery.

than plasma during resuscitation[26]. Clinically important outcomes differ when comparing physiologically balanced crystalloids with isotonic saline solution. In the past year, a study at a single ICU[27] and another in patients undergoing major abdominal surgery[28], compared outcomes based on "chloride load". Consistent with earlier preclinical and human studies[25-28], chloride restriction was found to be beneficial (Table 2). However, even large volume resuscitation with balanced crystalloid solutions is capable of inducing mild metabolic acidosis due to hemodilution of weak acids and relative changes in strong ion difference. The challenges with many balanced crystalloid solutions is that they contain small concentrations of calcium and additional electrolytes that theoretically increase the risk for precipitation or clot formation during co-administration with citrated blood products when compared with saline. However, 0.9% saline is non-physiologic and the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contributes to iatrogenic hyperchloremic metabolic acidosis. Indeed, the use of balanced crystalloid resuscitation in patients with diabetic ketoacidosis, despite the added (potassium) content [(K^+) 5.0 mmol/L], was associated with more rapid correction of base deficit when compared to 0.9% saline[49]. Recent data have also clearly shown high (chloride) solutions contribute to renal vasoconstriction, decreased glomerular filtration, greater interstitial fluid accumulation[29-34] along with increased risk of acute kidney injury (AKI) and utilization of renal replacement therapy (RRT)[35].

A CONCEPTUAL FRAMEWORK FOR FLUID MANAGEMENT

A novel conceptual framework for fluid management in critical illness introduces the idea of interrelated phases of fluid management differentiated according to the clinical status of the patient with evolving goals for fluid need[33] (Figure 1). The model proposed for the epidemiology of fluid balance in AKI may be extended across the spectrum of critical illness with caveats: (1) In the initial phase of acute resuscitation-the objective is restoration of effective circulating blood volume, organ perfusion and tissue oxygenation. Fluid accumulation and a positive fluid balance may be expected; (2) In the second phase of resuscitation-the goal is maintenance of intravascular volume homeostasis. The objective during this phase is to prevent excessive fluid accumulation and avoid unnecessary fluid loading; and (3) In the final stage, the objective centers around fluid removal and the concept of active "de-resuscitation" corresponding to a state of physiologic stabilization, organ injury recovery and convalescence. During this phase, unnecessary fluid accumulation may contribute to secondary organ injury and adverse events.

Table 3 Studies in critically ill patients describing the association with fluid overload and worse outcome

Study	Design	Population	Exposures	Outcomes
Pediatric Studies				
Goldstein *et al*[33]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Foland *et al*[60]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ organ dysfunction + mortality
Sutherland *et al*[31]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↑ mortality
Arikan *et al*[30]	Retrospective	Pediatric critically ill starting CRRT	% FO	↑ % FO associated with ↓ lung function
Adult Studies				
Payen *et al*[61]	Post-hoc prospective	Adult critically ill septic patients	FB	↑ FB associated with ↑ mortality
Murphy *et al*[62]	Retrospective	Adult critically ill ALI patients	AIFR + CLFM	↑ Survival for ↑ AIFR + ↑ CLFM
Bouchard *et al*[63]	Post-hoc prospective	Adult critically ill AKI patients	% FO > 10%	↑ FB associated with ↑ mortality
Wiedemann *et al*[36]	RCT	Adult critically ill with ALI	Conservative *vs* liberal fluid management strategy	↑ MV-free days; ↑ ICU-free days with conservative strategy
Fulop *et al*[64]	Retrospective	Adult critically ill starting CRRT	VRWG	↑ VRWG associated with ↑ mortality
Boyd *et al*[65]	Post-hoc analysis from VASST	Adult critically ill septic patients	Quartiles of FB + CVP at 12 h and 4 d	↑ FB at 12 h and 4 d associated with ↑ mortality; CVP < 8 at 12 h ↓ mortality
Grams *et al*[66]	Post-hoc FACCT	Adult critically ill with ALI + AKI	FB + diuretics	↑ FB associated with ↑ mortality
Heung *et al*[67]	Retrospective	Adult critically ill starting CRRT	% FO	↑ % FO associated with ↓ kidney recovery
Bellomo *et al*[68]	Post-hoc RENAL	Adult critically ill with AKI	FB	↑ FB associated with ↑ mortality

Adapted from Raghunathan *et al*[58]. ALI: Acute lung injury; AIFR: Adequate initial fluid resuscitation; CLFM: Conservative late fluid management; VRWG: Volume-related weight gain; AKI: Acute kidney injury; CVP: Central venous pressure; ICU: Intensive care unit; RCT: Randomized clinical trial.

Numerous studies in peri-operative and critical care settings support this concept of "ebb and flow" in fluid loading, fluid accumulation and removal. Indeed, these phases of resuscitation likely exist on a continuum and the observed variability in fluid balance is understood to be a dynamic process, does not necessarily follow a fixed temporal pattern or time scale and is likely highly individualized. For example, in septic patients with acute lung injury, the balance between early goal-directed therapy aimed at adequate initial fluid resuscitation coupled with downstream diuretic use and "de-resuscitation" (*i.e.,* conservative late fluid management) can improve outcomes[37,38]. Similarly in pediatric septic shock, outcome improved with early appropriate fluid therapy[39]. Such phasic need for fluid and then need for active fluid removal has also been demonstrated in peri-operative settings[40]. Inappropriate fluid therapy, regardless of fluid type, may disrupt compensatory mechanisms and worsen outcome[5].

QUANTITATIVE TOXICITY

Fluid therapy is a critical aspect of initial acute resuscitation in critically ill patients. Following the acute resuscitative phase (*i.e.,* achievement of immediate resuscitation goals and after hemodynamic stabilization), excessive fluid accumulation has been associated with worse clinical outcome, across a range in clinical settings, particularly in AKI[37] (Table 3). In patients with sepsis-associated AKI, continued fluid loading in the setting of apparent optimal systemic hemodynamics was shown not to improve kidney function, but worsen lung function and oxygenation[30]. Similar observational data in critically ill adults with sepsis-associated AKI has found fluid accumulation to be a predictor of 60-d mortality (HR = 1.21/L per 24 h, 95%CI: 1.13-1.28, $P < 0.001$)[37]. Additionally, although the FACCT trial did not demonstrate a mortality difference between a liberal and a more conservative fluid management strategy in the setting of acute lung injury, the conservative strategy was associated with improved lung function, reduced length of stay in ICU and a trend for lower utilization of RRT[36]. Increasing severity of fluid accumulation among both pediatric and adult patients with AKI at the time of initiation of RRT has been associated with higher mortality and reduced likelihood of recovery of kidney function[42-45]. For each 1% increase in percentage fluid overload (% FO, as calculated below) at RRT initiation, risk of death increased by 3%[31]. % FO = [(total fluid in-total fluid out)/admission body weight × 100].

Failure to appreciate these phases of fluid management following resuscitation may underscore the observed phenomenon of "fluid creep", first identified in the burn literature in response to the overwhelming enthusiasm for aggressive and sustained fluid resuscitation[29,32]. These observations highlight the importance of monitoring fluid balance in critical illness, in particular after the initial phase of resuscitation, where obligatory fluid intake (*i.e.,* medications, nutrition, blood products) may greatly exceed output (*i.e.,* relative oliguria), leading to rapid fluid accumulation[34]. In these circumstances, there should be effort to minimize or avoid all non-essential fluid administration. However, data on fluid accumulation in critically ill patients is almost entirely post-hoc, associative and not causal. Very few prospective interventional studies, with the exception of the FACCT trial and selected studies of conservative peri-operative fluid regimens have informed on the optimal fluid management strategies for critically ill patients and evaluated their association with organ function, adverse events, and survival[35,36]. This represents an important knowledge gap in our understanding of how to optimally manage-

Table 4 Summary of randomized trials of hydroxyethyl starch resuscitation in severe sepsis/septic shock and kidney outcomes

Ref.	RCT type	*n* (HES/CON)	Population (*n*)	HES fluid	Control fluid	Kidney parameters	RRT (OR; 95%CI)
Schortgen *et al*[50]	Multi-centre	129 (65/64)	Severe sepsis/ septic shock	6% (200/0.62)	3% gelatin	↑ AKI ↑ oliguria, ↑ peak SCr	1.20 (0.5-2.9)
Molnár *et al*[69]	Single centre	30 (15/15)	Septic shock	6% (200/0.60)	3% gelatin	NR	NR
McIntyre *et al*[70]	Multi-centre	40 (21/19)	Septic shock	6% (200/0.50)	0.9% NS	No difference	3.00 (0.3-31.6)
Brunkhorst *et al*[42]	Multi-centre	537 (262/275)	Severe sepsis/ septic shock	10% (200/0.5)	RL	↑ AKI	1.95 (1.3-2.9)
Guidet *et al*[23]	Multi-centre	196 (100/96)	Severe sepsis/ septic shock	6% (130/0.4)	0.9% NS	No difference	NR
Perner *et al*[6]	Multi-centre	798 (398/400)	Severe sepsis/ septic shock	6% (130/0.42)	Ringer's acetate	↑ AKI	1.35 (1.01-1.8)
Myburgh *et al*[5]	Multi-centre	7000 (3315/3336)	Sepsis (27.4%) (1921/7000)	6% (130/0.4)	0.9% NS	↑ RRT	1.21 (1.00-1.45)

RCT: Randomized clinical trial; HES: Hydroxyethyl starch; CON: Control; NS: Normal saline; RL: Ringer's lactate; AKI: Acute kidney injury; RRT: Renal replacement therapy; NR: Not report.

ment fluid beyond the initial resuscitation for acutely ill patients.

QUALITATIVE TOXICITY

Colloid solutions

The saline *vs* albumin fluid evaluation (SAFE) trial, in which nearly 7000 critically ill patients were randomized to either 4% human albumin or saline for resuscitation was the first large scale high-quality trial to show no overall difference in mortality, ICU length of stay, need for mechanical ventilation or RRT, or hospital length of stay. However, subgroup analyses founds trends for higher mortality in trauma patients, predominantly with head injury (OR = 1.36, $P = 0.06$) and lower mortality in sepsis (OR = 0.87, $P = 0.09$)[37]. Subsequently, a post-hoc longer-term follow-up study of patients enrolled in the SAFE trial who had suffered traumatic brain injury was performed, confirming the initial trends to suggest a higher mortality in head-injured patients receiving albumin (OR = 1.88, $P < 0.001$)[38].

While HES solutions, including newer starches, appear equally or more efficacious (*vs* older starches or crystalloids in certain situations) for restoration of intravascular volume in acute resuscitation, data continues to accumulate to suggest harm in critical illness (Table 4). Small clinical trials have suggested HES solutions are also superior for resuscitation of the microcirculation in sepsis and contribute to more rapid hemodynamic stabilization and shock reversal, and require significantly less fluid to restore intravascular volume. There has been suggestion of an improved safety profile for HES solutions with a lower molecular weight and lower degree of molar substitution, in terms of bleeding complications and AKI; however, these findings have been inconsistent. Prior to VISEP, 6S and CHEST, the literature had largely been dominated by small lower quality randomized trials that precluded a clear appraisal of potential survival benefit and the risk of toxicity[39,40]. In addition, wide scale retractions have followed reporting of fraud in research evaluating the safety of HES[41,46]. Accrued data from large randomized trials have now raised serious concerns about potential for dose-associated kidney toxic effects of HES[5,6,42,43]. Experimental data have shown even newer generation HES solutions can still accumulate in tissues within hours of administration, including in the liver, kidney, lung, spleen and lymph nodes[69]. In the VISEP trial, pentastarch (10% HES 200/0.5) was compared to Ringer's lactate for fluid resuscitation in ICU[42]. The trial was stopped early due to the increased incidence of AKI (34.9% *vs* 22.8%, $P = 0.001$) and a trend towards increased mortality (41% *vs* 33.8%, $P = 0.09$). These results were corroborated in the CHEST and 6S trials[5,6]. The CHEST trial evaluated the use of Voluven® (6% HES 130/0.4 in 0.9% saline) compared to 0.9% saline for acute resuscitation in ICU[5]. While there was no difference in mortality, there was an increase in the utilization of RRT (7.0% *vs* 5.8%, $P = 0.04$) in those receiving HES. In the 6S trial, Tetraspan® (6% HES 130/0.42 in Ringer's acetate) was compared to Ringer's lactate for acute resuscitation in severe sepsis[7]. Both the incidence of AKI (22% *vs* 16%, $P = 0.04$), and mortality (51% *vs* 43% at 90 d, $P = 0.03$) were significantly higher with HES. These data imply an increased risk for harm associated with HES solutions and have lead the European Society of Intensive Care Medicine to recommend against the use of HES in patients with severe sepsis or those at risk for AKI and has further suggested a moratorium on the use of HES except in the context of a clinical trial[49]. In addition, the United States Food and Drug Administration has recently issued black Boxed warning against their use in critically ill patients due to the increased risk of AKI and death[44]. However, there remains continued controversy on whether the use of HES in recent randomized trials was appropriate, such as only being used early and in limited volumes for the acute resuscitation of critically ill hypovolemic patients[45].

All HES solutions are carried in crystalloid. In the 6S trial, both arms received balanced crystalloid solution (*i.e.,* Ringer's acetate); whereas in the CHEST trial, both groups received 0.9% saline. It is biologically plausible there may be considerable interaction between the ad-

verse effects of HES and the chloride-rich 0.9% saline. When considering high chloride load is associated with adverse effects and worse outcome, it is therefore plausible that the harm associated with HES is exaggerated when used with 0.9% saline compared with a balanced crystalloid carrier.

In the 6S trial[6], patients were less likely to achieve shock reversal (*i.e.,* failure to clear lactate); whereas, in the CHEST trial[5], shock was reversed (*i.e.*, lactate cleared) with less total fluid administered in the HES group. These data imply that while HES may be more efficacious for shock resolution when compared to crystalloid; if there is delayed or failure to reverse shock, there may be greater toxicity and harm associated with HES; and this hazard may not be immediately apparent (*i.e.,* risk of harm is delayed several days to weeks).

The use of hyperoncotic colloid solutions for acute resuscitation remains controversial. In a large multi-centre European study of 822 critically ill adults with shock receiving fluid resuscitation, use of hypertonic natural and synthetic colloids was associated with a several fold increased risk for AKI and death[50]. A recent systematic review found divergent findings for use of hyperoncotic colloids for resuscitation and subsequent risk of AKI[51]. In this meta-analysis of 7 trials including 1220 patients, hyperoncotic albumin was associated with reduced risk (OR = 0.24, $P < 0.001$); whereas hyperoncotic HES solutions were associated with increased risk for AKI (OR = 1.92; 95%CI: 1.31-2.81, $P < 0.001$). These data seem to further infer the kidney toxicity may be a class effect associated with HES solutions.

Crystalloid solutions

The *iv* solution used in 1832 by Dr Thomas Latta for the treatment of cholera would today be considered a balanced salt solution: 134 mmol/L Na^+, 118 mmol/L Cl^-, 16 mmol/L HCO_3^-[52]. Surprisingly, it was not until 1888 that a reference to *normal* or *physiologic saline* is found in the medical literature, and not until 1896 that 0.9% saline is described[53,54]. Despite the fact that 0.9% sodium chloride is not isotonic to serum, it is believed that *in vitro* experiments comparing the freezing points of various solutions to serum led to the belief that this solution was "physiologic". Perhaps it was for simplicities' sake that solutions containing mixtures of anions were avoided in favor of the addition of table salt to water.

However, data are accumulating to suggest chloride-rich solutions are problematic. As aforementioned, the high (chloride) and a lower strong ion difference compared to plasma (0.9% saline: 0 mmol/L *vs* plasma: 40 mmol/L), directly contribute to iatrogenic hyperchloremic metabolic acidosis, which may mask, simulate and/or precipitate adverse effects[55,56]. In a randomized crossover trial of healthy volunteers, renal blood flow and renal cortical perfusion decreased significantly following the bolus administration of 2 L of 0.9% saline compared to plasma-lyte 148[30]. The use of chloride-rich solutions in critically ill patients is not only associated with increased costs and laboratory utilization[57], but also increased incidence of AKI and RRT utilization[27].

These observations are supported from a recent interrogation of the Premier perspective comparative database of patients undergoing elective or emergent open general surgical operations evaluating the rate of adverse events associated with receiving either balanced or isotonic saline solutions on the day of surgery[28]. In this study, patients who received exclusively a calcium-free balanced salt solution (plasma-Lyte A or plasma-Lyte 148) were matched on a 3:1 basis with those receiving exclusively 0.9% saline. Although there were no statistically significant differences between the two groups at baseline, the differences in outcome were dramatic: significantly fewer postoperative infections ($P = 0.006$), less dialysis ($P < 0.001$), fewer blood transfusions ($P < 0.001$), fewer electrolyte disturbances ($P = 0.046$), fewer acidosis investigations ($P < 0.001$) and interventions ($P = 0.02$) were all associated with the use of balanced salt solutions compared with 0.9% saline. While these data are not a randomized comparison of balanced *vs* 0.9% saline solutions, randomized trials are ongoing.

CONCLUSION

Despite its ubiquitous use in critical care, further carefully performed, transparent research on fluid resuscitation in critical illness is desperately needed. Context appears to be crucial when prescribing fluid and any fluid can be harmful if dosed incorrectly. Differences in immediate efficacy between crystalloid and colloid solutions are modest at best, but the differences in longer-term safety appear more significant. Qualitative toxicity for colloids (even with newer lower molecular weight, less substituted HES solutions) and isotonic saline remain a concern. The observed differences in chloride load and strong ion difference in the various crystalloid solutions appear to be clinically important. We contend that physiologically balanced crystalloids may be the best "default" fluid for acutely ill patients, and that the role of colloids is unclear. Optimal dosing of any resuscitation fluid mandates an understanding the dynamic nature of fluid resuscitation, and future investigations will hopefully allow for the development of better tools to guide therapy.

REFERENCES

1 **Lewins R**. Injection of saline solutions in extraordinary quantities into the veins in cases of malignant cholera. *Lancet* 1832, **18**: 243-244

2 The Cases of Cholera Successfully Treated. Lancet 1832: 18: 284

3 **Finfer S**, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care* 2010; **14**: R185 [PMID: 20950434 DOI: 10.1186/cc9293]

4 **Maitland K**, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; **364**: 2483-2495 [PMID: 21615299]

5 **Myburgh JA**, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901-1911 [PMID: 23075127 DOI: 10.1056/NEJMoa1209759]

6 **Perner A**, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124-134 [PMID: 22738085 DOI: 10.1056/NEJMoa1204242]

7 **Myburgh JA**. Fluid resuscitation in acute illness--time to reappraise the basics. *N Engl J Med* 2011; **364**: 2543-2544 [PMID: 21615300 DOI: 10.1056/NEJMe1105490]

8 **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]

9 **Jones AE**, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739-746 [PMID: 20179283 DOI: 10.1001/jama.2010.158]

10 **Jansen TC**, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; **182**: 752-761 [PMID: 20463176 DOI: 10.1164/rccm.200912-1918OC]

11 **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]

12 **Levitov A**, Marik PE. Echocardiographic assessment of preload responsiveness in critically ill patients. *Cardiol Res Pract* 2012; **2012**: 819696 [PMID: 21918726 DOI: 10.1155/2012/819696]

13 **Monnet X**, Teboul JL. End-tidal carbon dioxide and arterial pressure for predicting volume responsiveness by the passive leg raising test: reply to Piagnerelli and Biston. *Intensive Care Med* 2013; **39**: 1165 [PMID: 23615701 DOI: 10.1007/s00134-013-2920-1]

14 **Monnet X**, Bleibtreu A, Ferré A, Dres M, Gharbi R, Richard C, Teboul JL. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med* 2012; **40**: 152-157 [PMID: 21926581 DOI: 10.1097/CCM.0b013e31822f08d7]

15 **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]

16 **Cochrane Injuries Group Albumin Reviewers**. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317**: 235-240 [PMID: 9677209 DOI: 10.1136/bmj.317.7153.235]

17 **Mills H**. 300 die as health chiefs dither. London: Observer, 1998

18 **Dieterich HJ**, Weissmüller T, Rosenberger P, Eltzschig HK. Effect of hydroxyethyl starch on vascular leak syndrome and neutrophil accumulation during hypoxia. *Crit Care Med* 2006; **34**: 1775-1782 [PMID: 16625120 DOI: 10.1097/01.CCM.0000218814.77568.BC]

19 **Feng X**, Hu Y, Ding J, Ge Y, Song J, Ai Q, Zhang Z, Xu J. Early treatment with hydroxyethyl starch 130/0.4 causes greater inhibition of pulmonary capillary leakage and inflammatory response than treatment instituted later in sepsis induced by cecal ligation and puncture in rats. *Ann Clin Lab Sci* 2007; **37**: 49-56 [PMID: 17311869]

20 **Feng X**, Liu J, Yu M, Zhu S, Xu J. Protective roles of hydroxyethyl starch 130/0.4 in intestinal inflammatory response and survival in rats challenged with polymicrobial sepsis. *Clin Chim Acta* 2007; **376**: 60-67 [PMID: 16942763 DOI: 10.1016/j.cca.2006.07.008]

21 **Lang K**, Suttner S, Boldt J, Kumle B, Nagel D. Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. *Can J Anaesth* 2003; **50**: 1009-1016 [PMID: 14656778 DOI: 10.1007/BF03018364]

22 **Marx G**, Pedder S, Smith L, Swaraj S, Grime S, Stockdale H, Leuwer M. Resuscitation from septic shock with capillary leakage: hydroxyethyl starch (130 kd), but not Ringer's solution maintains plasma volume and systemic oxygenation. *Shock* 2004; **21**: 336-341 [PMID: 15179134 DOI: 10.1097/00024382-200404000-00008]

23 **Guidet B**, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care* 2012; **16**: R94 [PMID: 22624531 DOI: 10.1186/cc11358]

24 **Magder S**, Potter BJ, Varennes BD, Doucette S, Fergusson D. Fluids after cardiac surgery: a pilot study of the use of colloids versus crystalloids. *Crit Care Med* 2010; **38**: 2117-2124 [PMID: 20802322 DOI: 10.1097/CCM.0b013e3181f3e08c]

25 **Bullivant EM**, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol* 1989; **256**: F152-F157 [PMID: 2912160]

26 **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]

27 **Wilcox CS**. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; **71**: 726-735 [PMID: 6826732 DOI: 10.1172/JCI110820]

28 **Williams EL**, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 1999; **88**: 999-1003 [PMID: 10320158]

29 **Saffle JI**. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res* 2007; **28**: 382-395 [PMID: 17438489 DOI: 10.1097/BCR.0B013E318053D3A1]

30 **Arikan AA**, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012; **13**: 253-258 [PMID: 21760565]

31 **Sutherland SM**, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, Hackbarth R, Somers MJ, Baum M, Symons JM, Flores FX, Benfield M, Askenazi D, Chand D, Fortenberry JD, Mahan JD, McBryde K, Blowey D, Goldstein SL. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis* 2010; **55**: 316-325 [PMID: 20042260]

32 **Engrav LH**, Colescott PL, Kemalyan N, Heimbach DM, Gibran NS, Solem LD, Dimick AR, Gamelli RL, Lentz CW. A biopsy of the use of the Baxter formula to resuscitate burns or do we do it like Charlie did it? *J Burn Care Rehabil* 2000; **21**: 91-95 [PMID: 10752739 DOI: 10.1097/00004630-200021020-00

002]
33 **Goldstein SL**. Fluid Management in Acute Kidney Injury. *J Intensive Care Med* 2012 Nov 14; Epub ahead of print [PMID: 23753221]
34 **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]
35 **Brandstrup B**, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum 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]
36 **Wiedemann HP**, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, 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]
37 **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]
38 **Myburgh J**, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; **357**: 874-884 [PMID: 17761591 DOI: 10.1056/NEJMoa067514]
39 **Gattas DJ**, Dan A, Myburgh J, Billot L, Lo S, Finfer S. Fluid resuscitation with 6 % hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. *Intensive Care Med* 2013; **39**: 558-568 [PMID: 23407978]
40 **Hartog CS**, Skupin H, Natanson C, Sun J, Reinhart K. Systematic analysis of hydroxyethyl starch (HES) reviews: proliferation of low-quality reviews overwhelms the results of well-performed meta-analyses. *Intensive Care Med* 2012; **38**: 1258-1271 [PMID: 22790311 DOI: 10.1007/s00134-012-2614-0]
41 **Sessler DI**, Kurz A. Departmental and institutional strategies for reducing fraud in clinical research. *Anesth Analg* 2012; **115**: 474-476 [PMID: 22826524 DOI: 10.1213/ANE.0b013e3182580cbb]
42 **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, Kiehntopf 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]
43 **Raghunathan K**, Shaw A. Hydroxyethyl starch or saline in intensive care. *N Engl J Med* 2013; **368**: 774-775 [PMID: 23425177 DOI: 10.1056/NEJMc1215977]
44 **Food and Drug Administration**. Hydroxyethyl Starch Solutions: FDA Safety Communication - Boxed Warning on Increased Mortality and Severe Renal Injury and Risk of Bleeding. Available from: URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm358349.htm
45 **Meybohm P,** Van Aken H, De Gasperi A, De Hert S, Della Rocca G, Girbes AR, Gombotz H, Guidet B, Hasibeder W, Hollmann MW, Ince C, Jacob M, Kranke P, Kozek-Langenecker S, Loer SA, Martin CD, Siegemund M, Wunder C, Zacharowski K. Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl-starch in critically ill patients - a multidisciplinary statement. *Crit Care* 2013; **17**: R166 [PMID: 23890518 DOI: 10.1186/cc12845]
46 **Antonelli M**, Sandroni C. Hydroxyethyl starch for intravenous volume replacement: more harm than benefit. *JAMA* 2013; **309**: 723-724 [PMID: 23423420 DOI: 10.1001/jama.2013.851]
47 **Wilkes MM**, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. *Ann Thorac Surg* 2001; **72**: 527-33; discussion 534 [PMID: 11515893 DOI: 10.1016/S0003-4975(01)02745-X]
48 **O'Malley CM**, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg* 2005; **100**: 1518-124, table of contents [PMID: 15845718 DOI: 10.1213/01.ANE.0000150939.28904.81]
49 **Chua HR**, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, Kruger P, Bellomo R. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care* 2012; **27**: 138-145 [PMID: 22440386 DOI: 10.1016/j.jcrc.2012.01.007]
50 **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]
51 **Wiedermann CJ**, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M. Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials. *Crit Care* 2010; **14**: R191 [PMID: 21029460 DOI: 10.1186/cc9308]
52 **Awad S**, Allison SP, Lobo DN. The history of 0.9% saline. *Clin Nutr* 2008; **27**: 179-188 [PMID: 18313809 DOI: 10.1016/j.clnu.2008.01.008]
53 **Lazarus-Barlow WS**. On the Initial Rate of Osmosis of Blood-Serum with reference to the Composition of "Physiological Saline Solution" in Mammals. *J Physiol* 1896; **20**: 145-157 [PMID: 16992354]
54 **Churton E**. Leeds General Infirmary: A case of scirrhus of the pylorus, with excessive vomiting; repeated intravenous injections of saline solution; remarks. *Lancet* 1888; **132**: 620-621
55 **Shaw AD**, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012; **255**: 821-829 [PMID: 22470070 DOI: 10.1097/SLA.0b013e31825074f5]
56 **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]
57 **Yunos NM**, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011; **39**: 2419-2424 [PMID: 21705897 DOI: 10.1097/CCM.0b013e31822571e5]
58 **Raghunathan K**, Shaw AD, Bagshaw SM. Fluids are drugs: type, dose and toxicity. *Curr Opin Crit Care* 2013; **19**: 290-298 [PMID: 23817025 DOI: 10.1097/MCC.0b013e3283632d77]
59 **McFarlane C**, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia* 1994; **49**: 779-781 [PMID: 7978133 DOI: 10.1111/j.1365-2044.1994.tb04450.x]
60 **Foland JA**, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, Rogers K, Reid C, Tanner AJ, Easley KA. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Crit Care Med* 2004; **32**: 1771-1776 [PMID: 15286557 DOI: 10.1097/01.CCM.0000132897.52737.49]
61 **Payen D**, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. 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]

62 **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]
63 **Bouchard J**, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL. 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]
64 **Fülöp T**, Pathak MB, Schmidt DW, Lengvárszky Z, Juncos JP, Lebrun CJ, Brar H, Juncos LA. Volume-related weight gain and subsequent mortality in acute renal failure patients treated with continuous renal replacement therapy. *ASAIO J* 2010; **56**: 333-337 [PMID: 20559136]
65 **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.0b013e3181feeb15]
66 **Grams ME**, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6**: 966-973 [PMID: 21393482 DOI: 10.2215/CJN.08781010]
67 **Heung M**, Wolfgram DF, Kommareddi M, Hu Y, Song PX, Ojo AO. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. *Nephrol Dial Transplant* 2012; **27**: 956-961 [PMID: 21856761 DOI: 10.1093/ndt/gfr470]
68 **Bellomo R**, Cass A, Cole L, Finfer S, Gallagher M, Lee J, Lo S, McArthur C, McGuiness 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]
69 **Molnár Z**, Mikor A, Leiner T, Szakmány T. Fluid resuscitation with colloids of different molecular weight in septic shock. *Intensive Care Med* 2004; **30**: 1356-1360 [PMID: 15127186 DOI: 10.1007/s00134-004-2278-5]
70 **McIntyre LA**, Fergusson D, Cook DJ, Rankin N, Dhingra V, Granton J, Magder S, Stiell I, Taljaard M, Hebert PC. Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. *Can J Anaesth* 2008; **55**: 819-826 [PMID: 19050085 DOI: 10.1007/BF03034053]

P- Reviewers: Chang HT, Moschovi M **S- Editor**: Zhai HH
L- Editor: A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.34

World J Crit Care Med 2014 February 4; 3(1): 34-41
ISSN 2220-3141 (online)

META-ANALYSIS

Ulinastatin for acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis

Yu-Xin Leng, Shu-Guang Yang, Ya-Han Song, Xi Zhu, Gai-Qi Yao

Yu-Xin Leng, Shu-Guang Yang, Xi Zhu, Gai-Qi Yao, Department of Intensive Care Unit, Peking University Third Hospital, Beijing 100191, China
Ya-Han Song, Library of Peking University Third Hospital, Beijing 100191, China
Author contributions: Leng YX and Yang SG contributed to literature search and study selection; Leng YX and Song YH contributed to data extraction, analysis and interpretation; Yao GQ, Zhu X and Yao GQ contributed to study conception and design; Leng YX drafted the article; Yao GQ revised the article critically for important intellectual content.
Correspondence to: Gai-Qi Yao, MD, PhD, Associate Professor, Department of Intensive Care Unit, Peking University Third Hospital, A 49 North Garden Rd., Haidian District, Beijing 100191, China. yaogaiqi@yeah.net
Telephone: +86-10-82267280 Fax: +86-10-82267281
Received: June 5, 2013 Revised: October 5, 2013
Accepted: November 2, 2013
Published online: February 4, 2014

Abstract

AIM: To investigate the efficacy and safety of ulinastatin for patients with acute lung injury (ALI) and those with acute respiratory distress syndrome (ARDS).

METHODS: A systematic review of randomized controlled trials (RCTs) of ulinastatin for ALI/ARDS was conducted. Oxygenation index, mortality rate [intensive care unit (ICU) mortality rate, 28-d mortality rate] and length of ICU stay were compared between ulinastatin group and conventional therapy group. Meta-analysis was performed by using Rev Man 5.1.

RESULTS: Twenty-nine RCTs with 1726 participants were totally included, the basic conditions of which were similar. No studies discussed adverse effect. Oxygenation index was reported in twenty-six studies (1552 patients). Ulinastatin had a significant effect in improving oxygenation [standard mean difference (SMD) = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$, $I^2 = 92\%$]. ICU mortality and 28-d mortality were respectively reported in eighteen studies (987 patients) and three studies (196 patients). We found that ulinastatin significantly decreased the ICU mortality [$I^2 = 0\%$, RR = 0.48, 95%CI: 0.38-0.59, number needed to treat (NNT) = 5.06, $P < 0.00001$], while the 28-d mortality was not significantly affected ($I^2 = 0\%$, RR = 0.78, 95%CI: 0.51-1.19, NNT = 12.66, $P = 0.24$). The length of ICU stay (six studies, 364 patients) in the ulinastatin group was significantly lower than that in the control group (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$, $I^2 = 86\%$).

CONCLUSION: Ulinastatin seems to be effective for ALI and ARDS though most trials included were of poor quality and no information on safety was provided.

Key words: Ulinastatin; Acute lung injury; Acute respiratory distress syndrome; Mortality; Oxygenation index

Core tip: Currently, many studies highlight the advantages of ulinastatin in lung protection, which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. We tried to provide more specific evidence on this practice by performing a meta-analysis. In our study (29 clinical trials included), we found that though all the studies were of low quality, ulinastatin might improve oxygenation and mortality and be truly effective in patients with ALI/ARDS.

Leng YX, Yang SG, Song YH, Zhu X, Yao GQ. Ulinastatin for acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *World J Crit Care Med* 2014; 3(1): 34-41 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/34.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.34

INTRODUCTION

Ulinastatin, also known as human urinary trypsin inhibitor, can be found in urine, plasma and all organs[1]. It is a glycoprotein marketed as an experimental medication for acute pancreatitis and septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process[2-5]. Currently, many animal studies and clinical trials highlight its advantages in lung protection[6-38], which is likely because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis, which is systemic inflammatory response syndrome. However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS. Without the support of large-scale, high-quality trials, it is difficult to draw a definite conclusion. Therefore, we perform a systematic review to evaluate the efficacy and safety of ulinastatin for ALI and ARDS to provide more specific evidence.

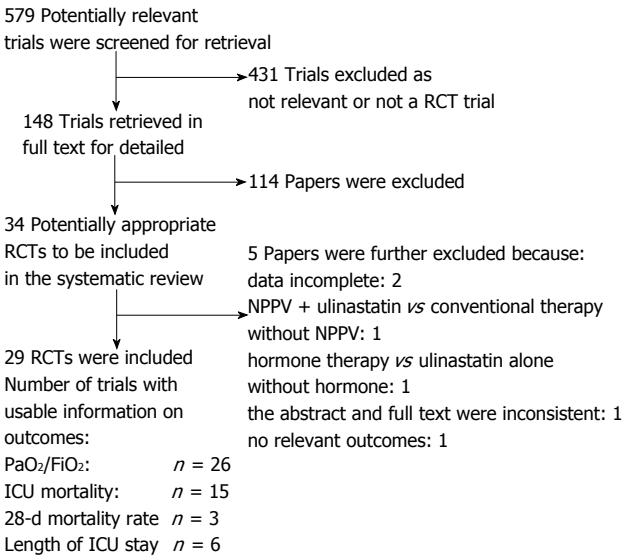


Figure 1 Flow chart of reviewed articles. RCT: Randomized controlled trial; NPPV: Noninvasive positive-pressure ventilation; ICU: Intensive care unit.

MATERIALS AND METHODS

Search strategy

We searched the published randomized controlled trials (RCTs) (from 1st January 2006 to 20th August 2012) from eight databases including Pubmed, Medline (Ovid SP), The Cochrane Library, Wanfang Database, China Biology Medicine Database, Chinese Periodical Database, China Knowledge Resource Integrated Database and Chinese Clinical Trial Registry with the following search terms: "Ulinastatin" or "Protease-Inhibitors" or "Glycoprotein" and "Acute Respiratory Distress Syndrome" or "ARDS" or "Acute Lung Injury" or "ALI". There were no language restrictions on inclusive studies. All potentially relevant papers based on titles and abstracts were retrieved for full text screening. We also collected relevant articles by checking the references of the retrieved papers.

Study selection

Both the study selection (Leng YX, Song YF) and data extraction processes (Leng YX, Yang SG) were performed by two authors independently. Disagreements were resolved by group discussion. Figure 1 showed the flow chart of study selection process.

We included the RCT studies comparing ulinastatin plus routine treatment (treatment group) versus routine treatment alone or placebo plus routine treatment (control group) for ALI and ARDS. ALI and ARDS were diagnosed as: acute onset; pulmonary artery wedge pressure $\leqslant$ 18 mmHg or absence of clinical evidence of left atrial hypertension; bilateral infiltrates on chest radiography; ALI is present if PaO_2/FiO_2 ratio is $\leqslant$ 300; ARDS is present if PaO_2/FiO_2 ratio $\leqslant$ 200. Any dose and duration of ulinastatin were permitted. The outcomes included intensive care unit (ICU) mortality rate or PaO_2/FiO_2 ratio.

Data extraction and quality assessment

The following parameters were extracted from each inclusive study: (1) first author and year of the publication; (2) patients' characteristics and study design; and (3) clinical outcomes (ICU mortality, 28-d mortality, PaO_2/FiO_2 ratio, length of ICU stay and adverse effect). The quality of all selected articles was evaluated according to the Jadad scale[39], which bases on the random assignment, double blinding, and flow of patients. The range of score is 0 (bad) to 5 (good).

Statistical analysis

Meta-analysis was conducted using RevMan 5.1 software. For dichotomous variables (ICU mortality, 28-d mortality) we estimated the pooled risk ratios (RRs) and 95%CI. For continuous variables (PaO_2/FiO_2 ratio and length of ICU stay), we calculated the estimation of standard mean difference (SMD). Heterogeneity was explored by the I^2 test. If $I^2 < 50\%$, the fixed-effect model (Mantel-Haenszel) was employed, otherwise the random-effect model (DerSimonian and Laird) was used. The significance of pooled RR was determined by Z test. $P < 0.05$ was considered statistically significant. Funnel plots were used to detect the potential publication bias if more than ten studies were included. The sensitivity analysis was conducted by taking each single study away from the total and re-analyzing the remainder.

RESULTS

Study characteristics

After full text screening, 34 potentially relevant studies were identified. Among these studies, five were excluded because there were incomplete data (1 study), other interventions besides ulinastatin were included (2 studies), the abstract and full text were inconsistent (1 study), and no relative outcomes were reported (1 study) (Figure 1). Finally, 29 studies involving 1726 participants were included[10-38], the basic conditions of which were similar. The conventional therapy included mechanical ventila-

Table 1 Quality and characteristics of all included studies

Ref.	Yr	Jadad score	Design	Sample size	Gender (male/female)	Age (yr, mean or range)	Dosage	Frequency	Duration (d)	Outcomes
Chen *et al*[10]	2006	1	NRCT	70	40/30	36.6	200000	*bid*	2-7	Oxygenation index
Gu *et al*[11]	2011	1	NRCT	120	65/55	56.2	100000	*tid*	5	Oxygenation index
Hu *et al*[12]	2009	1	NRCT	54	39/15	41.2	300000	*tid*	7	Oxygenation index Length of ICU stay 28-d mortality rate
Huang *et al*[13]	2010	1	NRCT	80	41/39	49	100000	*tid*	5	Oxygenation index Length of ICU stay ICU Mortality rate
Jiang *et al*[14]	2006	1	NRCT	57	32/25	58.1	200000	*qd*	7-10	Oxygenation index ICU Mortality rate
Liang *et al*[15]	2011	1	NRCT	62	36/26	38.8	200000	*bid*	7	Oxygenation index Length of ICU stay
Liang *et al*[16]	2008	1	NRCT	76	42/34	57	200000	*bid*	6	Oxygenation index ICU Mortality rate
Lu *et al*[17]	2008	1	NRCT	60	42/18	39.7	50000	*qd*	3	Oxygenation index
Ou *et al*[18]	2008	1	NRCT	36	24/12	63.7	200000-300000	*bid*	5-7	Oxygenation index ICU Mortality rate Incidence of MODS
Pi *et al*[19]	2009	1	NRCT	40	25/15	37	200000-	*bid*	5-7	Incidence of MODS ICU Mortality rate
Qian *et al*[20]	2009	1	NRCT	48	35/13	48	200000	*qid*	6	Oxygenation index ICU Mortality rate Length of ICU stay
Qin[21]	2007	1	NRCT	60	40/20	35	300000	*bid*	3	Oxygenation index
Shang *et al*[22]	2008	2	RCT	60	48/12	14-72	200000	*tid*	7	Oxygenation index ICU Mortality rate
Shi *et al*[23]	2011	1	NRCT	50	34/16	59.4	300000	*bid*	7-10	Oxygenation index ICU Mortality rate
Wang *et al*[24]	2011	1	NRCT	52	32/20	55.4	200000	*tid*	10	ICU Mortality rate
Wang *et al*[25]	2011	1	NRCT	60	44/16	18-60	200000	*bid*	5	Oxygenation index
Xiang *et al*[26]	2011	1	NRCT	72	46/26	46.8	200000	*tid*	7	Oxygenation index
Xiong[27]	2008	1	NRCT	50	28/22	35	300000	*bid*	7	Oxygenation index
Yang *et al*[28]	2011	1	NRCT	40	NA	NA	200000	*tid*	10	Oxygenation index
Yang *et al*[29]	2006	2	NRCT	80	58/22	14-72	300000	*bid*	7	Oxygenation index ICU Mortality rate
Zhang *et al*[30]	2009	1	NRCT	34	22/12	9-61	200000	*tid*	10	Oxygenation index ICU Mortality rate
Zhang *et al*[31]	2011	1	NRCT	82	43/39	18-65	200000	*bid*	7	Oxygenation index 28-d mortality rate
Zhang[32]	2010	2	RCT	60	45/15	43.3	300000	*bid*	7	Oxygenation index
Zhang *et al*[33]	2010	1	RCT	60	30/30	55.7	500000	*bid*	7	Oxygenation index Length of ICU stay 28-d mortality rate
Zhang *et al*[34]	2009	1	NRCT	61	54/7	61.9	200000	*bid*	7	Oxygenation index
Zhao *et al*[35]	2012	2	RCT	56	37/19	46.2	200000	*bid*	4	Oxygenation index
Zhao *et al*[36]	2007	1	NRCT	37	29/8	42.6	100000	*bid*	5	Oxygenation index ICU Mortality rate
Zheng *et al*[37]	2011	1	NRCT	60	42/18	40.2	50000	*qd*	3	Oxygenation index ICU mortality rate
Zhou *et al*[38]	2011	1	NRCT	40	NA	40.2	600000	*qid*	5	Length of ICU stay Oxygenation index ICU Mortality rate

NA: Not available; NRCT: Non-randomized controlled trial; RCT: Randomized controlled trial; ICU: Intensive care unit.

tion, low dose hormone, nutritional support, treatment of primary diseases, *etc*. Of the included studies, no one discussed the adverse effect of ulinastatin. Oxygenation index was reported in 26 studies (1552 patients). Eighteen studies (987 patients) and three studies (196 patients) analyzed the ICU mortality and 28-d mortality, respectively. The length of ICU stay was reported in six studies (364 patients). Although all the trials announced the randomization, only four studies mentioned the allocation concealment without detailed description of mechanisms. Table 1 displays the quality and characteristics of these studies.

Oxygenation index

The basal oxygenation indexes in all studies were similar. After treatment with standard strategy or ulinastatin, the patients' oxygenation indexes were improved in all studies. The effect of ulinastatin was more significant (Figure

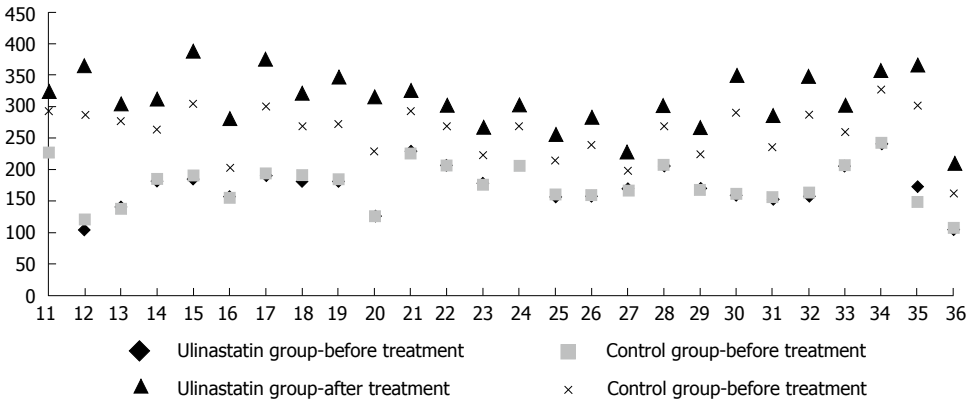


Figure 2 Oxygenation indexes of different groups before and after treatment. The horizontal axis, number of references.

2), which was confirmed by the meta-analysis (SMD = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$, $I^2 = 92\%$, Figure 3A).

Mortality rate

Most studies (15/18) reported that the ICU mortality rate was not significantly different between ulinastatin treatment and conventional treatment. The 95%CI crossed 1.00. Nevertheless, the result of meta-analysis indicated that ulinastatin actually reduced the patients' ICU mortality rate, and the pooled RR was 0.48 (95%CI: 0.38-0.59, $I^2 = 0\%$, Figure 3B). The number needed to treat (NNT) was 5.06. However, the 28-d mortality was not significantly different between the two groups (RR = 0.78, 95%CI: 0.51-1.19, $I^2 = 0\%$, Figure 4A), and the NNT was 12.66.

Length of ICU stay

Five of the six studies reporting the length of ICU stay suggested that compared with conventional therapy, ulinastatin significantly decreased the length of ICU stay, which was confirmed by the result of meta-analysis (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$, $I^2 = 86\%$, Figure 4B).

Publication bias and sensitivity analysis

Funnel plots of ICU mortality and oxygenation index are shown in Figure 5, which indicated that the publication bias did exist. The language bias may be the main bias because all the inclusive studies were written in Chinese. The sensitivity analysis showed that exclusion of any single study from the meta-analysis did not alter the overall conclusion. Though I^2 of the oxygenation index and ICU stay were larger than 50%, we considered that those heterogeneities were probably related to great difference among studies.

DISCUSSION

ARDS is a common severe lung complication with direct and indirect causes in ICU. In the past 20 years, the mortality rate decreased from 40%-70% to 30%-40%. This survival improvement is considered to be partly related with the better understanding and treatment of sepsis[40]. Since ulinastatin is marketed as an experimental medication for septic shock, the probable efficacy of ulinastatin for ALI and ARDS gains more and more attention.

It is reported that ulinastatin inhibits pathogenic changes in animal models of ALI/ARDS induced by many factors (including scald, seawater, LPS, phosgene)[6-9]. Immunoregulation and the mitigation of excessive inflammatory reaction might be involved. Downregulation of the human major histocompatibility complex class I chain-related antigen A (MICA), mitigation of lipid peroxidation and apoptosis may play important roles. Upregulation of MICA in scald induced lung injury can be ameliorated by ulinastatin[6]. Moreover, ulinastatin treatment can reduce the level of cytokines like serum E, P-selectin and VCAM-1, which are considered to be critical in the development of inflammatory responses[41]. Nevertheless, the effect of ulinastatin on pulmonary injury and the molecular mechanism(s) by which ulinastatin exerts its organ-protective activity remain obscurely studied. In addition, clinical trials also recommended application of ulinastatin for ALI/ARDS though no high quality evidence was reported. Only one meta-analysis on ulinastatin for ALI/ARDS was reported till now[42], in which only Chinese databases were detected. Accordingly, we yet have no enough evidence to support the recommendation of ulinastatin for ALI/ARDS. We performed this meta-analysis to evaluate the existing clinical trials objectively and to provide more specific evidence for ulinastatin selection for ALI/ARDS.

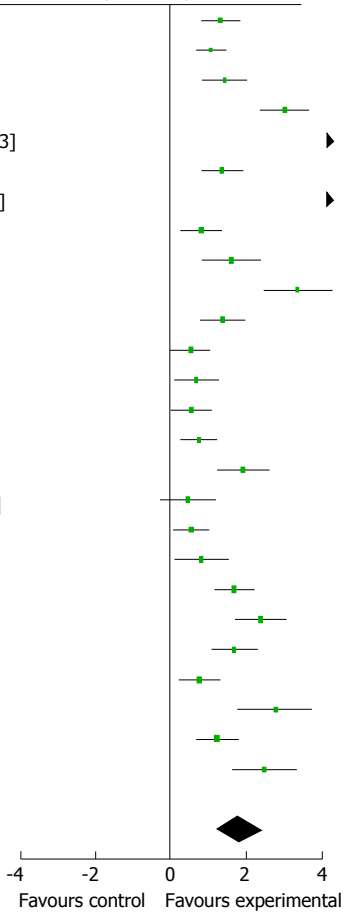
Our results seem to be inspiring. Compared with routine treatment alone, ulinastatin plus routine treatment significantly improved the oxygenation index (SMD = 1.85, 95%CI: 1.42-2.29, $P < 0.00001$) and reduced the ICU mortality rate (RR = 0.48, 95%CI: 0.38-0.59, NNT = 5.06, $P < 0.00001$) and the length of ICU stay (SMD = -0.97, 95%CI: -1.20--0.75, $P < 0.00001$). Nevertheless, the validity of this meta-analysis to some extent is limited. No studies reported the adverse effect. Most of the clinical trials were of poor quality without description of randomization and allocation mechanisms. Meanwhile, the language bias is introduced in this review, because all the included trials were published in Chinese. Then, how should we interpret these clinical trials and the systematic review based on these trials? Should the clinical

A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, Random, 95%CI
Chen HD 2006	326	25	35	294	23	35	4.1%	1.32 [0.80, 1.84]
Gu ZY 2011	364.42	56.21	60	286.56	86.54	60	4.2%	1.06 [0.68, 1.44]
Hu MH 2009	305.67	18.31	29	276.93	21.23	25	4.0%	1.44 [0.83, 2.04]
Huang YP 2010	309	16	40	263	14	40	4.0%	3.03 [2.38, 3.68]
Jiang XQ 2006	389.59	5.77	29	305.28	4.95	28	1.4%	15.45 [12.46, 18.43]
Liang DS 2011	282.08	53.43	31	203.34	60.83	31	4.1%	1.36 [0.80, 1.91]
Liang QX 2008	378	6.92	39	300	7.82	37	2.5%	10.47 [8.71, 12.24]
Lu WH 2011	322.63	56.71	30	267.82	75.66	30	4.1%	0.81 [0.28, 1.34]
Ou SQ 2008	347.75	48.56	18	272.62	42.77	18	3.8%	1.61 [0.84, 2.37]
Qian HB 2009	311.9	18.4	24	228.3	29.2	24	3.7%	3.37 [2.47, 4.27]
Qin XW 2007	327.03	24.98	30	293.28	22.95	30	4.1%	1.39 [0.82, 1.96]
Shang GJ 2008	303.25	57.64	30	269	68.92	30	4.1%	0.53 [0.02, 1.05]
Shi QJ 2011	265.78	65.95	25	223.58	57.26	25	4.1%	0.67 [0.10, 1.24]
Wang KM 2011	303.85	57.6	30	268.98	68.82	30	4.1%	0.54 [0.03, 1.06]
Xiang JF 2011	256	58	36	214	51	36	4.1%	0.76 [0.28, 1.24]
Xiong SS 2008	286.15	21.23	25	238.96	26.78	25	3.9%	1.92 [1.24, 2.60]
Yang JB 2011	228.55	67.56	15	198.23	56.78	15	3.9%	0.47 [-0.25, 1.20]
Yang K 2006	303.3	57.6	40	269	68.9	40	4.2%	0.53 [0.09, 0.98]
Zhang BM 2009	266.5	45.7	17	224.4	55.3	17	3.9%	0.81 [0.11, 1.51]
Zhang CQ 2010	352.1	38.8	42	291.2	31.6	40	4.1%	1.70 [1.19, 2.21]
Zhang RW 2010	288.1	19.1	30	236.1	23.4	30	4.0%	2.40 [1.73, 3.08]
Zhang YL 2009	350.2	40.1	31	287.4	32.2	30	4.0%	1.70 [1.11, 2.29]
Zhao HQ 2012	304.27	53.54	28	259.09	61.72	28	4.1%	0.77 [0.23, 1.32]
Zhao RG 2007	356.45	10.92	18	327.08	9.57	16	3.6%	2.78 [1.81, 3.76]
Zheng JM 2011	362.42	40.57	30	302.25	55.37	30	4.1%	1.22 [0.67, 1.78]
Zhou MH 2011	206.78	17.68	20	161.06	18.2	20	3.7%	2.50 [1.65, 3.34]
Total (95%CI)			782			770	100.0%	1.85 [1.42, 2.29]

Heterogeneity: Tau^2 = 1.13; χ^2 = 325.20, df = 25 (P = 0.00001); I^2 = 92%

Test for overall effect: Z = 8.36 (P = 0.00001)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95%CI
Hu MH 2009	5	29	6	25	3.5%	0.72 [0.25, 2.07]
Huang YP 2010	10	40	20	40	10.7%	0.50 [0.27, 0.93]
Jiang XQ 2006	7	29	20	28	10.9%	0.34 [0.17, 0.67]
Liang DS 2011	2	31	7	31	3.8%	0.29 [0.06, 1.27]
Liang QX 2008	10	39	22	37	12.1%	0.43 [0.24, 0.78]
Ou SQ 2008	3	18	9	18	4.8%	0.33 [0.11, 1.03]
Pi Y 2010	3	20	9	20	4.8%	0.33 [0.11, 1.05]
Qian HB 2009	6	24	8	24	4.3%	0.75 [0.31, 1.83]
Shang GJ 2008	4	30	11	30	5.9%	0.36 [0.13, 1.01]
Shi QJ 2011	2	25	8	25	4.3%	0.25 [0.06, 1.06]
Wang CB 2011	3	26	7	26	3.8%	0.43 [0.12, 1.48]
Yang K 2006	4	40	11	40	5.9%	0.36 [0.13, 1.05]
Zhang BM 2009	2	17	5	17	2.7%	0.40 [0.09, 1.78]
Zhang CG 2011	10	42	12	40	6.6%	0.79 [0.39, 1.63]
Zhang CQ 2010	11	30	14	30	7.5%	0.79 [0.43, 1.44]
Zhao RG 2007	5	19	8	18	4.4%	0.59 [0.24, 1.47]
Zheng JM 2011	1	23	3	22	1.6%	0.32 [0.04, 2.84]
Zhou MH 2011	2	18	4	16	2.3%	0.44 [0.09, 2.11]
Total (95%CI)		500		487	100.0%	0.48 [0.38, 0.59]
Total events	90		184			

Heterogeneity: χ^2 = 10.13, df = 17 (P = 0.90); I^2 = 0%

Test for overall effect: Z = 6.76 (P = 0.00001)

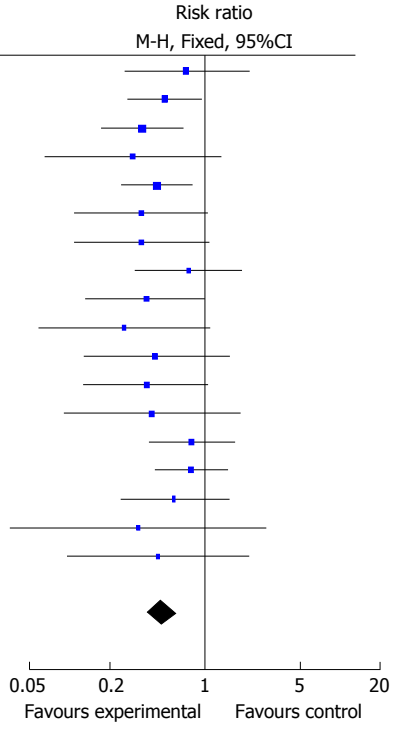


Figure 3 Meta-analysis of patients' oxygenation index (A) and intensive care unit mortality rate (B) after treatment with conventional therapy *vs* with ulinastatin (random effects). A: Random effects model; B: Fixed effects model.

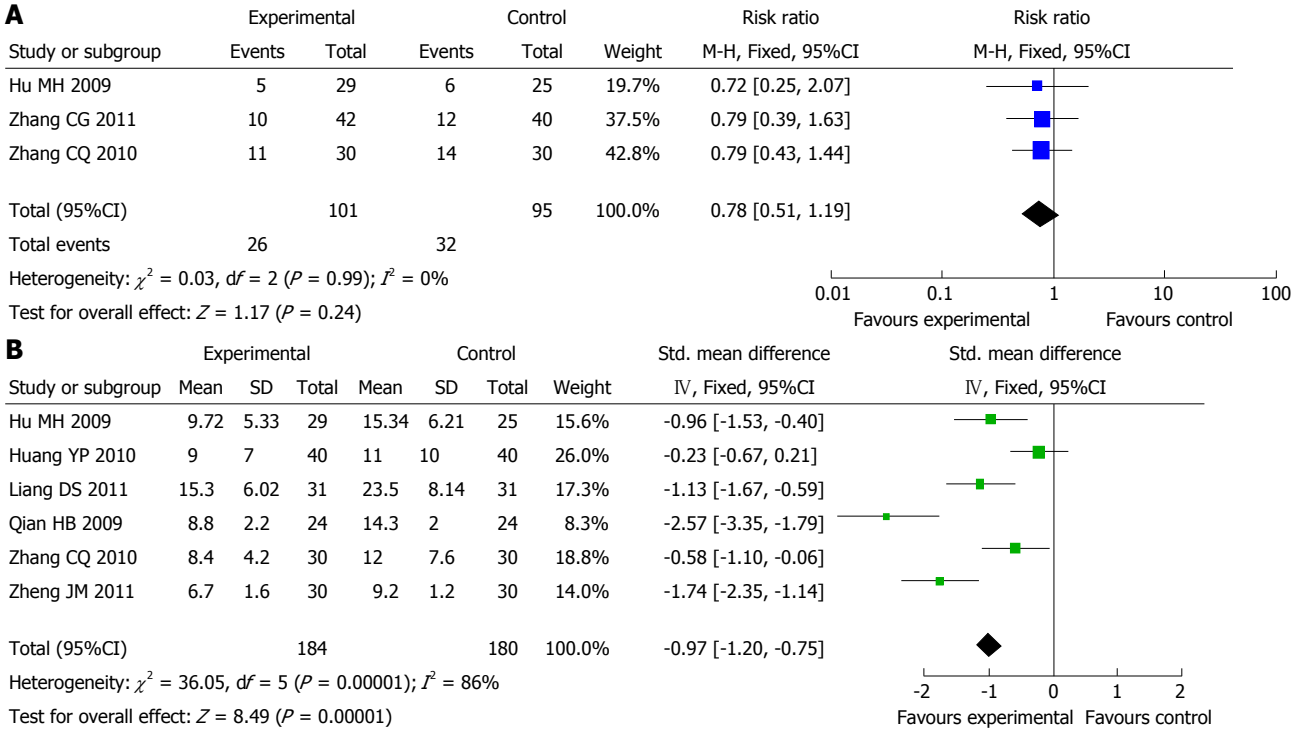


Figure 4 Meta-analysis of 28-d mortality rate (A) and length of intensive care unit stay (B) between treatment with conventional therapy and with ulinastatin. A: Fixed effects model; B: Random effects model.

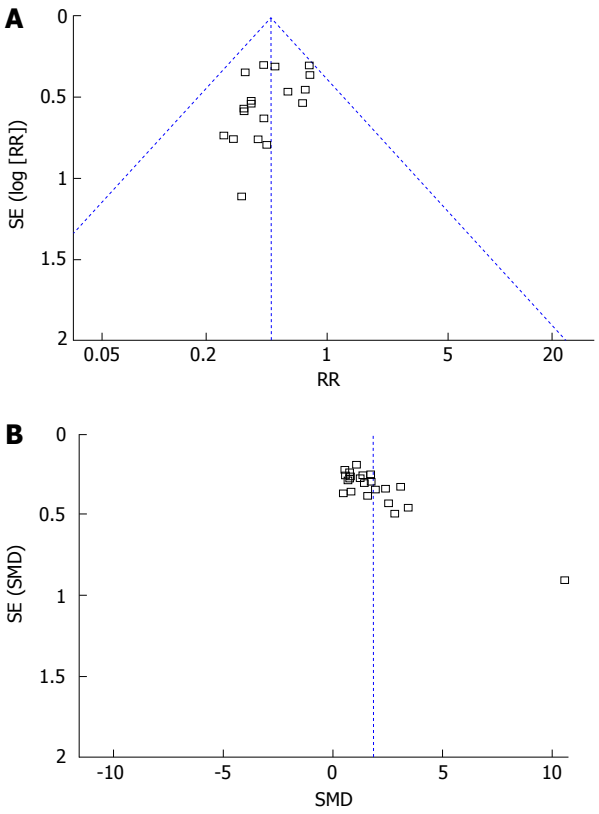


Figure 5 Funnel plots of intensive care unit mortality (A) and oxygenation index (B). SMD: Standard mean difference.

practitioners consider ulinastatin as a first-line treatment? Obviously, we can not draw a definite conclusion right now. Although ulinastatin seems to be effective for ALI/ARDS, high-quality RCTs discussing the efficacy and safety are needed in the future.

COMMENTS

Background

Ulinastatin is marketed as an experimental medication for septic shock in Asia for its involvement in suppressing the systemic inflammation and proteolytic process. Currently, many studies highlight its advantages in lung protection, which is because acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) share a common pathogenesis with sepsis. However, it remains uncertain whether ulinastatin can be recommended as a standard medication for ALI and ARDS.

Research frontiers

No large-scale randomized controlled trials (RCTs) studies or high quality meta-analysis on ulinastatin for ALI and ARDS were performed till now. Whether the application of ulinastatin in ALI and ARDS is appropriate remains unclear.

Innovations and breakthroughs

To provide more specific evidence for clinical practice, the authors performed a meta-analysis on ulinastatin for ALI and ARDS.

Applications

This study indicated that ulinastatin might be truly effective for ALI and ARDS though most RCT studies included were of poor quality.

Peer review

The authors conducted a systematic review and meta-analysis of the retrieved studies on the effects of ulinastatin on ALI and ARDS. The paper is essentially well written, and provides some information.

REFERENCES

1 **Pugia MJ**, Lott JA. Pathophysiology and diagnostic value of urinary trypsin inhibitors. *Clin Chem Lab Med* 2005; **43**: 1-16 [PMID: 15653436 DOI: 10.1515/CCLM.2005.001]

2 **Ohnishi H**, Kosuzume H, Ashida Y, Kato K, Honjo I. Effects of urinary trypsin inhibitor on pancreatic enzymes and experimental acute pancreatitis. *Dig Dis Sci* 1984; **29**: 26-32

[PMID: 6363018 DOI: 10.1007/BF01296858]
3 **Uemura K**, Murakami Y, Hayashidani Y, Sudo T, Hashimoto Y, Ohge H, Sueda T. Randomized clinical trial to assess the efficacy of ulinastatin for postoperative pancreatitis following pancreaticoduodenectomy. *J Surg Oncol* 2008; **98**: 309-313 [PMID: 18548482 DOI: 10.1002/jso.21098]
4 **Cao YZ**, Tu YY, Chen X, Wang BL, Zhong YX, Liu MH. Protective effect of Ulinastatin against murine models of sepsis: inhibition of TNF-α and IL-6 and augmentation of IL-10 and IL-13. *Exp Toxicol Pathol* 2012; **64**: 543-547 [PMID: 21159497 DOI: 10.1016/j.etp.2010.11.011]
5 **Inoue K**, Takano H. Urinary trypsin inhibitor as a therapeutic option for endotoxin-related inflammatory disorders. *Expert Opin Investig Drugs* 2010; **19**: 513-520 [PMID: 20367192 DOI: 10.1517/13543781003649533]
6 **Gao C**, Liu Y, Ma L, Wang S. Protective effects of ulinastatin on pulmonary damage in rats following scald injury. *Burns* 2012; **38**: 1027-1034 [PMID: 22455798 DOI: 10.1016/j.burns.2012.02.004]
7 **Shen J**, Gan Z, Zhao J, Zhang L, Xu G. Ulinastatin reduces pathogenesis of phosgene-induced acute lung injury in rats. *Toxicol Ind Health* 2012 Oct 16; Epub ahead of print [PMID: 23075575 DOI: 10.1177/0748233712463776]
8 **Rui M**, Duan YY, Zhang XH, Wang HL, Wang DP. Urinary trypsin inhibitor attenuates seawater-induced acute lung injury by influencing the activities of nuclear factor-κB and its related inflammatory mediators. *Respiration* 2012; **83**: 335-343 [PMID: 22179035 DOI: 10.1159/000333378]
9 **Fang Y**, Xu P, Gu C, Wang Y, Fu XJ, Yu WR, Yao M. Ulinastatin improves pulmonary function in severe burn-induced acute lung injury by attenuating inflammatory response. *J Trauma* 2011; **71**: 1297-1304 [PMID: 21926648 DOI: 10.1097/TA.0b013e3182127d48]
10 **Chen HD**, Zhuo Y. The clinical effect of Ulinastatin intravenous for acute lung injury (ALI). *Linchuang Feike Zazhi* 2006; **11**: 252-253 [DOI: 10.3969/j.issn.1009-6663.2006.02.083]
11 **Gu ZY**, Tian HY. The influence of Ulinastatin on plasma NO and endothelin-1 in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). *Zhonghua Linchuang Yishi Zazhi* 2011; **5**: 190-191 [DOI: 10.3877/ema.j.issn.1674-0785.2011.04.06]
12 **Hu MH**, Xu XJ, Jin D, Ji CL, Chen YB, Zhang G. The influence of ulinastatin on endothelial permeability in patients with ARDS. *Quanke Yixue Linchuang Yu Jiaoyu* 2009; **7**: 229-231 [DOI: 10.3969/j.issn.1672-3686.2009.03.009]
13 **Huang YP**, Xu XP, Wang XJ, Li MX, Pan RF. Clinical observation on the treatment of acute lung Injury with protective mechanical ventilation in combination with ulinastatin. *Hebei Yixue* 2010; **16**: 783-786 [DOI: 10.3969/j.issn.1006-6233.2010.07.006]
14 **Jiang XQ**, Wang YS, Wang SJ, Hu JC, Song DB. The efficacy of ulinastatin on protective ventilated patients with acute lung injury. *Zhongguo Jijiu Yixue* 2006; **26**: 161-163 [DOI: 10.3969/j.issn.1002-1949.2006.03.001]
15 **Liang DS**, Du ZL, Zeng H. Clinical studies of 31 cases on the treatment of ulinastatin for patients with acute lung injury. *Guangxi Yike Daxue Xuebao* 2011; **28**: 125-126 [DOI: 10.3969/j.issn.1005-930X.2011.01.044]
16 **Liang QX**, Wei GX, Yan XM. The efficacy of ulinastatin with protective ventilation in patients with acute lung injury. *Youjiang Yixue* 2008; **36**: 7-9 [DOI: 10.3969/j.issn.1003-1383.2008.01.003]
17 **Lu WH**, Xu XY, Tang ZZ, Chen ZQ, Cheng Q. The efficacy of ulinastatin in patients with traumatic acute lung injury. *Linchuang Junyi Zazhi* 2008; **36**: 863-865
18 **Ou SQ**, Yu M, Wen YM, Tao Y. Clinical study on treatment of acute respiratory distress syndrome (ARDS) with ulinastatin. *Chongqing Yixue* 2008; **37**: 1336-1337 [DOI: 10.3969/j.issn.1671-8348.2008.12.035]
19 **Pi Y**, Gui WF, Gu XL, Dai LX, Xiao ZY. Clinical study on treatment of ALI/ARDS induced by thoracic trauma with Ulinastatin. *Shandong Yiyao* 2009; **49**: 98-99 [DOI: 10.3969/j.issn.1002-266X.2009.46.050]
20 **Qian HB**, Zheng ZQ, Lu JH, Guan GH, Pu QH. Clinical study on therapy of ARDS caused by pulmonary contusion with ulinastatin. *Zhongguo Weizhongbing Jijiu Yixue* 2009; **21**: 444-445 [DOI: 10.3760/cma.j.issn.1003-0603.2009.07.021]
21 **Qin XW**. Clinical study of therapy of acute lung injury with ulinastatin. *Zhonghua Neike Zazhi* 2007; **2**: 552-553 [DOI: 10.3969/j.issn.1673-7768.2007.04.048]
22 **Shang GJ**, Nie ZX, Wang SZ. Clinical studies of 30 cases on the treatment of ulinastatin for patients with acute lung injury. *Zhongwai Yiliao* 2008; **30**: 117-118 [DOI: 10.3969/j.issn.1674-0742.2008.30.099]
23 **Shi QJ**, Yang ZP, Ma SQ. Clinical study on therapy of acute lung injury (ALI) with ulinastatin in XiNing. *Qinghai Yiyao Zazhi* 2011; **41**: 5-7
24 **Wang CB**, Tang Y,Li J, Xia CQ. Observation of the efficacy of ulinastatin on acute lung injury/acute respiratory distress syndrome. *Zhongguo Yiyao Daobao* 2011; **8**: 71-72 [DOI: 10.3969/j.issn.1673-7210.2011.29.031]
25 **Wang KM**, SunYH, Hou YQ. The clinical observation of ulinastatin for the patients with acute lung injury. *Zhongguo Shiyong Yiyao* 2011; **6**: 11-12 [DOI: 10.3969/j.issn.1673-7555.2011.15.006]
26 **Xiang JF**, Yang X, Gong JF. The influence of ulinastatin on respiratory mechanics and oxidative stress in ALI/ARDS patients. *Shandong Yiyao* 2011; **51**: 79-80 [DOI: 10.3969/j.issn.1002-266X.2011.05.050]
27 **Xiong SS**. The efficacy of ulinastatin on patients with acute lung injury. *Shiyong Linchuang Yixue* 2008; **9**: 34-37 [DOI: 10.3969/j.issn.1009-8194.2008.12.014]
28 **Yang JB**, Zhong ZL, Yang JY, Ye CL. The efficacy of ulinastatin on acute lung injury/acute respiratory distress. *Neimenggu Zhongyiyao* 2011; **5**: 82-83 [DOI: 10.3969/j.issn.1006-0979.2011.10.100]
29 **Yang K**, Shen JS, Zhang QS. Clinical study of 40 cases on the treatment of ulinastatin for patients with acute lung injury induced by trauma. *Zhongguo Jijiu Yixue* 2006; **26**: 229-230 [DOI: 10.3969/j.issn.1002-1949.2006.03.030]
30 **Zhang BM**, Sun Y, Xu JL, Pan LP. Ulinastatin for treatment of acute lung injury/acute respiratory distress syndrome: an analysis of 34 cases. *Bengbu Yixueyuan Xuebao* 2009; **34**: 1108-1110 [DOI: 10.3969/j.issn.1000-2200.2009.12.022]
31 **Zhang CG**, Jiang X, Liu SG. The influence of ulinastatin on oxygenation index and mortality rate in patients with ARDS. *Hainan Yixue* 2011; **22**: 8-10 [DOI: 10.3969/j.issn.1003-6350.2011.16.003]
32 **Zhang RW**. The effect of ulinastatin and dexamethasone on patients with traumatic acute lung injury. *Zhejiang Chuangshang Waike* 2010; **15**: 283-284 [DOI: 10.3969/j.issn.1009-7147.2010.03.005]
33 **Zhang CQ**, Wang YY, Gao ZZ, Hong F, Nie WQ, Wang LM. The effect of ulinastatin on the prognosis of patiens with ARDS. *Zhongguo Linchuang Shiyong Yixue* 2010; **4**: 18-20 [DOI: 10.3760/cma.j.issn 1673-8799.2010.03.09]
34 **Zhang YL**, Pan LW, Zhuang R, Lin MX, Ying BY, Ruan HY. The influence of ulinastatin on matrix metalloproteinase-2 and c-reactive protein in patients wiith traumatic ARDS. *Zhejiang Chuangshang Waike* 2009; **14**: 6-8 [DOI: 10.3969/j.issn.1009-7147.2009.01.003]
35 **Zhao HQ**, Lu K, Yuan KW, Dai ZD, Tian JH, Wang CY. The efficacy of ulinastatin on patients with acute cervical spinal cord injury accompanied acute lung injury. *Shiyong Yiyao Zazhi* 2012; **29**: 223-224 [DOI: 10.3969/j.issn.1671-4008.2012.03.019]
36 **Zhao RG**, Lin H, Zhang MH. The influence of ulinastatin on the expression of platelet activating factor in patients with acute lung injury (ALI). *Zhejiang Linchuang Yixue* 2007; **9**: 439-440 [DOI: 10.3969/j.issn.1008-7664.2007.04.004]
37 **Zheng JM**, Liu DL, Yang LJ. Clinical studies of 30 cases on ulinastatin for patients with acute lung injury. *Shanxi Yixue*

Zazhi 2011; **40**: 1516-1518 [DOI: 10.3969/j.issn.1000-7377.2011.11.031]

38 **Zhou MH**, Ren GL, Jiao FF. The clinical study of ulinastatin on patients with acute respiratory distress syndrome. *Binzhou Yixueyuan Xuebao* 2011; **34**: 122-124 [DOI: 10.3969/j.issn.1001- 9510. 2011.02.014]

39 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]

40 **Eloise MH**, Michael RP. Acute Respiratory Distress Syndrome. Medscape, 2012-03-19. Available from: URL: http://emedicine.medscape.com/article/165139-overview

41 **Koga Y**, Fujita M, Tsuruta R, Koda Y, Nakahara T, Yagi T, Aoki T, Kobayashi C, Izumi T, Kasaoka S, Yuasa M, Maekawa T. Urinary trypsin inhibitor suppresses excessive superoxide anion radical generation in blood, oxidative stress, early inflammation, and endothelial injury in forebrain ischemia/reperfusion rats. *Neurol Res* 2010; **32**: 925-932 [PMID: 20223106 DOI: 10.1179/016164110X12645013515133]

42 **Wu J**, Li P. Ulinastatin for Acute Lung Injury and Acute Respiratory Distress Syndrome: A Systematic Review. *Herald of Med* 2009; **28**: 302-304 [DOI: 10.3870/yydb.2009.03.010]

P- Reviewers: Chen HI, Pappas KT **S- Editor**: Zhai HH
L- Editor: Wang TQ **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.42

World J Crit Care Med 2014 February 4; 3(1): 42-44
ISSN 2220-3141 (online)

CASE REPORT

Failure of lorazepam to treat alprazolam withdrawal in a critically ill patient

Gaurav Sachdev, Gail Gesin, A Britton Christmas, Ronald F Sing

Gaurav Sachdev, Gail Gesin, A Britton Christmas, Ronald F Sing, The F H Sammy Ross, Jr Trauma Center, Department of Pharmacy, Carolinas Medical Center, Charlotte, NC 28023, United States
Ronald F Sing, Department of Surgery/MEB 601, Carolinas Medical Center, Charlotte, NC 28203, United States
Author contributions: Sing RF planned the study and was responsible for the design, collection of data, and initial draft of the manuscript; Sachdev G was responsible for author coordination, data interpretation, and final drafting of the manuscript; Gesin G and Christmas AB helped draft the manuscript; all authors read and approved the final manuscript.
Correspondence to: Ronald F Sing, DO, Department of Surgery/MEB 601, Carolinas Medical Center, 1000 Blythe Boulevard, Charlotte, NC 28203,
United States. ron.sing@carolinashealthcare.org
Telephone: +1-704-3553176 Fax: +1-704-3555619
Received: May 10, 2013 Revised: October 12, 2013
Accepted: November 15, 2013
Published online: February 4, 2014

Abstract

Management of sedation in the critical care unit is an ongoing challenge. Benzodiazepines have been commonly used as sedatives in critically ill patients. The pharmacokinetic and pharmacodynamic properties that make benzodiazepines effective and safe in critical care sedation include rapid onset of action and decreased respiratory depression. Alprazolam is a commonly used benzodiazepine that is prescribed for anxiety and panic disorders. It is frequently prescribed in the outpatient setting. Its use has been reported to result in a relatively high rate of dependence and subsequent withdrawal symptoms. Symptoms of alprazolam withdrawal can be difficult to recognize and treat in the critical care setting. In addition, other benzodiazepines may also be ineffective in treating alprazolam withdrawal. We present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam and haloperidol. Subsequent replacement with alprazolam resulted in significant improvement in the patient's medication use and clinical status.

Key words: Alpralazom; Lorazepam; Withdrawal; Pharmacokinetics; Pharmacodynamics

Core tip: Withdrawal from drugs and alcohol is a common phenomenon in the intensive care unit. Benzodiazepines are commonly used for both alcohol and benzodiazepine withdrawal. The pharmacokinetics and pharmacodynamics among drugs within this class vary. The failure of lorazepam to treat withdrawal of alprazolam is demonstrated in this case study.

Sachdev G, Gesin G, Christmas AB, Sing RF. Failure of lorazepam to treat alprazolam withdrawal in a critically ill patient. *World J Crit Care Med* 2014; 3(1): 42-44 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i1/42.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i1.42

INTRODUCTION

Benzodiazepines have been commonly used as sedatives in critically ill patients and also used extensively in the treatment of depression, anxiety, and panic disorders[1]. Key pharmacokinetic and pharmacodynamic properties of benzodiazepines include a rapid onset of action, decreased respiratory depression, higher ratio of lethal dose to effective dose, and a greater therapeutic dose margin between anxiolysis and sedation.

Alprazolam is a commonly used benzodiazepine for anxiety and panic disorders. It has been reported to have a relatively high occurrence of dependence and withdrawal symptoms[2,3]. Symptoms of alprazolam withdrawal can be difficult to recognize and treat in the critical care setting. In addition, other benzodiazepines may be

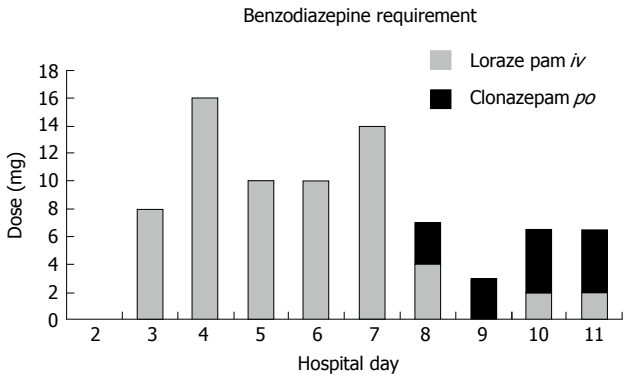


Figure 1 Dosages of lorazepam and clonazepam: hospital days 2-11.

ineffective in treating alprazolam withdrawal. We present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam.

CASE REPORT

A 28-year-old male was involved in a motor vehicle crash. After assessment and stabilization in the trauma bay he was noted to have an altered level of consciousness, mild traumatic brain injury with small subarachnoid hemorrhage, grade Ⅱ splenic laceration and ethanol level of 221 mg/dL. The patient required emergent splenic artery embolization for a decreasing hematocrit. Subsequently, he was admitted to the trauma intensive care unit and started on an alcohol withdrawal protocol which included lorazepam administered on an as needed symptom-directed schedule.

By hospital day 3, the patient became extremely agitated requiring multiple doses of intravenous lorazepam (2 mg times four doses) (Figure 1). Over the next 5 d, the patient required escalating doses of lorazepam to control his agitation (2 mg 6-7 times per day). Symptoms necessitating pharmacologic intervention included tachycardia, hypertension, confusion, slurred speech and pulling of his catheter and naso-enteric feeding tube.

On hospital day 8, a family member reported that the patient takes alprazolam 1 mg by mouth three times daily as a home medication. Following discussion with the clinical pharmacist member of the multi-professional critical care team, the patient was immediately started on clonazepam 1 mg three times a day. Following the first dose of clonazepam at noon, the patient received only one as needed dose of lorazepam that evening. On hospital day nine, no *as needed* lorazepam doses were required and only one was administered on hospital day 10. Despite an improving mental status, the patient remained confused. Thus, lorazepam was discontinued and the clonazepam dose was increased to 1.5 mg three times daily. On hospital day eleven, the patient again became acutely agitated and received lorazepam and multiple doses of haloperidol. By hospital day thirteen, his clonazepam was increased to 2 mg three times a day. The patient was less agitated and was transferred to an intermediate care unit.

Although improved, the patient remained restless and intermittently agitated. He required haloperidol 3 mg three times a day to control his agitation. Over the next 2 wk, the patient did not require any as needed benzodiazepines or haloperidol for acute agitation. The scheduled haloperidol was tapered and discontinued by discharge at hospital day 25. The clonazepam dose was tapered by 50% each week, and the patient was discharged to a rehabilitation facility on clonazepam 0.5 mg twice daily.

DISCUSSION

In comparison to other benzodiazepines, alprazolam may be associated with a higher propensity for addiction and result in more severe withdrawal symptoms. The prevalence of rebound anxiety is higher with benzodiazepines that have a short to intermediate half-life compared to those with a long half-life[4,5]. The effectiveness of other benzodiazepines at treating alprazolam withdrawal has been studied. The triazole ring found in alprazolam may have a significantly greater binding affinity for a subgroup of benzodiazepine receptors in areas of the brain that are not generally influenced by other benzodiazepines[6]. A review of eight case reports of alprazolam withdrawal published between 1984 and 1986 combined with six unpublished cases reported to the manufacturer provide early evidence of unique properties related to this agent. Chlordiazepoxide and diazepam were both found to be ineffective in preventing withdrawal symptoms in two separate cases. This review has been cited as providing clinical evidence to suggest that there is incomplete cross-tolerance between alprazolam and other benzodiazepines[7]. More recent review has shown that despite over prescription of benzodiazepines, withdrawal and dependence can be reduced by shorter duration prescriptions and withdrawal can be prevented by judicious weaning[8].

Differentiating withdrawal symptoms from pre-hospital substance use from those associated with the physiologic response to trauma can be difficult in critically ill patients since they are similar. In this patient, confusion, slurred speech, restlessness, and hypertension were thought to be related to alcohol withdrawal and tachycardia was presumed to be a presenting sign of a splenic bleeding. Although the patient was appropriately started on a symptom-directed alcohol withdrawal protocol at the time of admission, lorazepam was not effective in abating his agitation.

Lorazepam was clearly ineffective in treating this patient's alprazolam withdrawal. This is consistent with a previous report of a critically ill patient who exhibited alprazolam withdrawal despite large doses of lorazepam and diazepam[9]. Initiation of clonazepam on hospital day eight was associated with a reduction in lorazepam requirements (Figure 1). Although clonazepam was used, it is likely that alprazolam would have also been effective as a rapid response is often observed with reinstitution of the drug[4,5]. Clonazepam was chosen because it has an intermediate to long half-life ranging from 17-60 h and is associated with less rebound anxiety and withdrawal symptoms in comparison to shorter acting agents such as

alprazolam[4,5]. Furthermore, it has been used successfully for the management of alprazolam detoxification. This substitution in alprazolam-dependent patients has been shown to be safe and effective[5,10].

Given the unique characteristics and pharmacodynamics properties of alprazolam, reinstitution of this medication or substitution with clonazepam on a milligram per milligram basis are the preferred management strategies for trauma patients admitted with a history of pre-hospital alprazolam use to prevent withdrawal. Furthermore, consideration should be given to the high potential for therapeutic failure of other benzodiazepines in this patient population. This approach may prevent confusion with physiologic responses to injury and reduce the overall benzodiazepine requirement. This report highlights the need for obtaining an accurate medication history, as well as recognizing the physiologic effects related to injury, substance withdrawal, and medication administration. As such, we recommend a multi-professional approach with input from physicians, nurses, and clinical pharmacists to optimize these processes.

COMMENTS

Case characteristics

The authors present a case of alprazolam withdrawal in a critically ill trauma patient who failed treatment with lorazepam and haloperidol.

Clinical diagnosis

After assessment and stabilization in the trauma bay he was noted to have an altered level of consciousness, mild traumatic brain injury with small subarachnoid hemorrhage, grade Ⅱ splenic laceration and ethanol level of 221 mg/dL.

Differential diagnosis

The patient required emergent splenic artery embolization for a decreasing hematocrit.

Treatment

The patient was admitted to the trauma intensive care unit and started on an alcohol withdrawal protocol which included lorazepam administered on an as needed symptom-directed schedule.

Related reports

It has been used successfully for the management of alprazolam detoxification. This substitution in alprazolam-dependent patients has been shown to be safe and effective.

Experiences and lessons

This report highlights the need for obtaining an accurate medication history, as well as recognizing the physiologic effects related to injury, substance withdrawal, and medication administration.

Peer review

The authors well explained the failure of lorazepam to treat alprazolam withdrawal. This manuscript reports a case report on failure of lorazepam to treat alprazolam withdrawal in a critically ill trauma patient. The reason for this was well explained. Clonazepam was effective in the patient.

REFERENCES

1 **Barr J**, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263-306 [PMID: 23269131 DOI: 10.1097/CCM.0b013e3182783b72]

2 **Klein E**. The role of extended-release benzodiazepines in the treatment of anxiety: a risk-benefit evaluation with a focus on extended-release alprazolam. *J Clin Psychiatry* 2002; **63** Suppl 14: 27-33 [PMID: 12562116]

3 **Trevor AJ**, Way WL. Sedative-hypnotic drugs. In: Katzung BG, editor. Basic and Clinical Pharmacology, 6th edition. East Norwalk, CT: Appleton & Lange, 1995: 333-349

4 **Chouinard G**. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *J Clin Psychiatry* 2004; **65** Suppl 5: 7-12 [PMID: 15078112]

5 **Patterson JF**. Withdrawal from alprazolam dependency using clonazepam: clinical observations. *J Clin Psychiatry* 1990; **51** Suppl: 47-49; discussion 50-53 [PMID: 2335501]

6 **Browne JL**, Hauge KJ. A review of alprazolam withdrawal. *Drug Intell Clin Pharm* 1986; **20**: 837-841 [PMID: 3536383]

7 **Albeck JH**. Withdrawal and detoxification from benzodiazepine dependence: a potential role for clonazepam. *J Clin Psychiatry* 1987; **48** Suppl: 43-49 [PMID: 2889723]

8 **Ashton H**. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry* 2005; **18**: 249-255 [PMID: 16639148 DOI: 10.1097/01.yco.0000165594.60434.84]

9 **Freda JJ**, Bush HL, Barie PS. Alprazolam withdrawal in a critically ill patient. *Crit Care Med* 1992; **20**: 545-546 [PMID: 1559372]

10 **Patterson JF**. Alprazolam dependency: use of clonazepam for withdrawal. *South Med J* 1988; **81**: 830-831, 836 [PMID: 3393938]

P- Reviewer: Lee MG **S- Editor**: Zhai HH
L- Editor: A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
www.wjgnet.com

World J Crit Care Med 2014 February 4; 3(1): I-V
ISSN 2220-3141 (online)

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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 (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

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. The current columns of *WJCCM* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

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 basic and clinical significance.

WJCCM is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial borad members or peer reivewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJCCM* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in critical care medicine; (12) Brief Articles: To briefly report the novel and innovative findings in critical care medicine; (13) Meta-Analysis: Covers the systematic review, mixedtreatment comparison, meta-regression, and overview of reviews, in order to summarize a given quantitative effect, e.g., the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJCCM*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of critical care medicine; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

Launch date

February 4, 2012

Frequency
Quarterly

Instructions to authors
Full instructions are available online at http://www.wjgnet.com/2220-3141/g_info_20100722180909.htm.

Indexed and Abstracted in
Digital Object Identifier.

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJCCM* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory ani-

mals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2220-3141/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjccm@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, *e.g.*, Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, *e.g.*, Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, *e.g.*, 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned

clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P <$ 0.05, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, *e.g.*, PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2220-3141/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2220-3141/g_info_20100725073726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2220-3141/g_info_20100725073445.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

STATEMENT ABOUT ANONYMOUS PUBLICATION OF THE PEER REVIEWERS' COMMENTS

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

PUBLICATION FEE

WJCCM is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. All invited articles are published free of charge.

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2014 May 4; 3(2): 45-67

Baishideng Publishing Group
www.wjgnet.com

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 3 Number 2 May 4, 2014

World Journal of Critical Care Medicine
Volume 3 Number 2 May 4, 2014

Contents

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.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

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: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-6555-7188
Telephone: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
May 4, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3141/g_info_20100722180909.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i2.45

World J Crit Care Med 2014 May 4; 3(2): 45-54
ISSN 2220-3141 (online)

REVIEW

Metabolic theory of septic shock

Jay Pravda

Jay Pravda, Inflammatory Disease Research Centre, West Palm Beach, FL 33420, United States
Author contributions: Pravda J is the sole author of this manuscript and solely responsible for its content; Pravda J performed all the research, collected, analyzed and interpreted all the data; Pravda J conceived of and developed the Metabolic Theory of Septic Shock; Pravda J prepared and wrote the manuscript and performed all critical revisions; Pravda J certifies that the Metabolic Theory of Septic Shock is the product of his original research and Pravda J has overall responsibility for this manuscript.
Correspondence to: Jay Pravda, MD, MPH, Inflammatory Disease Research Centre, West Palm Beach, P.O. Box 32632, FL 33420, United States. jaypravda@yahoo.com
Telephone: +1-682-2513030 Fax: +1-888-7005813
Received: October 29, 2013 Revised: January 21, 2014
Accepted: March 3, 2014
Published online: May 4, 2014

Abstract

Septic shock is a life threatening condition that can develop subsequent to infection. Mortality can reach as high as 80% with over 150000 deaths yearly in the United States alone. Septic shock causes progressive failure of vital homeostatic mechanisms culminating in immunosuppression, coagulopathy and microvascular dysfunction which can lead to refractory hypotension, organ failure and death. The hypermetabolic response that accompanies a systemic inflammatory reaction places high demands upon stored nutritional resources. A crucial element that can become depleted early during the progression to septic shock is glutathione. Glutathione is chiefly responsible for supplying reducing equivalents to neutralize hydrogen peroxide, a toxic oxidizing agent that is produced during normal metabolism. Without glutathione, hydrogen peroxide can rise to toxic levels in tissues and blood where it can cause severe oxidative injury to organs and to the microvasculature. Continued exposure can result in microvascular dysfunction, capillary leakage and septic shock. It is the aim of this paper to present evidence that elevated systemic levels of hydrogen peroxide are present in septic shock victims and that it significantly contributes to the development and progression of this frequently lethal condition.

Key words: Septic shock; Hydrogen peroxide; Hypermetabolic; Sepsis; Systemic inflammatory response syndrome

Core tip: For decades septic shock has been attributed to an over-active immune response. However, immune modulation has failed to reduce mortality, casting doubt on a direct causal role for the immune response in the development of septic shock. A closer look suggests that septic shock is the result of a generalized build-up of hydrogen peroxide, a toxic cellular by-product generated as a consequence of the hypermetabolic state that accompanies a systemic immune response. This finding points to the systemic accumulation of hydrogen peroxide as a significant risk factor for the development of septic and non-septic shock syndromes.

Pravda J. Metabolic theory of septic shock. *World J Crit Care Med* 2014; 3(2): 45-54 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i2/45.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i2.45

INTRODUCTION

Sepsis is a life threatening condition that is associated with a systemic inflammatory response to a microbial infection[1]. Sepsis is the most common cause of mortality in the intensive care unit with a fatality rate that can rise to 80% for those developing multiple organ failure. The progression of an exaggerated systemic inflammatory response is thought to be responsible for the eventual development of septic shock and death[2]. However, multiple therapeutic efforts aimed at controlling the immune

response with the intent of interrupting the process leading to organ failure have been uniformly unsuccessful[1]. This simple fact has prompted a reappraisal of the role played by the immune system in the development of this condition that kills more than 150000 Americans yearly; more than breast, colon, prostate and brain cancer combined[3,4].

Although immune activation is clearly evident, recent evidence suggests that the immune response may not be the direct mediator of the pathologic process that leads to septic shock. Studies conducted to define the circulating leukocyte transcriptome have revealed that there is no qualitative difference in the immunogenetic response when comparing burn or blunt trauma patients with complicated or uncomplicated outcomes. In other words, severely injured patients who die from their injuries have the same immunogenetic response as patients who recover; the only difference being the duration and intensity of systemic inflammation[5].

The lack of a unique immunogenetic response suggests that septic shock is the phenotypic expression of a separate process that is initiated simultaneously with systemic immune activation. The multiple organ involvement, which can lead to death within a few days, suggests that this concomitant process is systemic in nature and initiated in parallel with inflammatory response. Moreover, the microvascular edema associated with multiple organ failure, which persists despite efforts at immunosuppression, suggests that a non-immune mediated angiopathic agent is being released into the systemic circulation[1].

The high (8%) increased mortality rate for each hour of delay before instituting antibiotics after the onset of hypotension suggests that the duration of this parallel process is closely linked with a greater risk of an adverse outcome and down regulating the immune response with successful therapy simply allows this parallel process to turn off[6].

In other words, survival is closely correlated with the early down regulation of a systemic process closely linked to systemic immune activation suggesting depletion of a crucial biochemical element that is critical for survival. Put differently, if catabasis (immune down regulation) is achieved by successful antibiotic therapy prior to depletion of this critical element the patient will survive, if not the patient is at high risk for organ failure, septic shock and death.

HYPERMETABOLIC RESPONSE

A key systemic process that is turned on and up-regulated with systemic inflammation is cellular metabolism, which becomes hypermetabolic from the onset of sepsis[7]. The sustained high fever, highly amplified protein synthesis, tachycardia and tachypnea characteristic of a septic immune response requires supra-physiological energy supplies. It is estimated that basal energy requirements for a septic patient can reach up to 10000 calories daily[8]. This hypermetabolic state not only requires increased nutrient intake but also generates a large amount of toxic cellular by-products as a result of increased electron transport chain (ETC) activity required to synthesize sufficient adenosine triphosphate (ATP) to support a prolonged hypermetabolic state. This critical need for supplemental nutrients often cannot be met as it occurs at a time when caloric intake is curtailed as a result of the severe illness afflicting the patient[8]. This suggests the progressive depletion of an element whose principal function is to metabolize a toxic cellular waste product that, upon accumulation, leads to organ dysfunction, microangiopathic edema and refractory hypotension, the characteristic pathologic findings in septic shock.

An important toxic product that is continuously generated as a result of cellular metabolism is hydrogen peroxide (H_2O_2), which is formed as a result of several metabolic activities including protein synthesis (disulfide bond formation), DNA recycling (Xanthine oxidase), ATP synthesis (ETC activity) and fatty acid oxidation (peroxisomal metabolism)[9-12]. Most H_2O_2 is degraded to water via the enzymatic action of glutathione peroxidase (GPx), a selenium containing enzyme that has an obligate requirement for the co-factor glutathione (GSH) in order to metabolize H_2O_2. The biochemical reaction is: $2\ GSH + H_2O_2 \rightarrow GS\text{-}SG + 2H_2O$ in which two molecules of GSH are converted to one molecule of glutathione disulfide (GS-SG) and two molecules of water. Glutathione is consumed during this process and must be replenished in order for the cell to prevent accumulation of H_2O_2 to toxic levels[13,14].

Replenishment of glutathione, however, is not favored during periods of sustained hypermetabolism and caloric insufficiency, which frequently accompany critical illnesses such as sepsis leading to depletion of glutathione reserves.

Within 48 h of diagnosis critically ill children with sepsis were found to have a 60% decrease in whole blood GSH synthesis, suggesting depletion of whole body GSH stores[15,16]. Systemic GSH depletion is supported by studies showing over 50% decrease in lung and skeletal muscle GSH in septic and critically ill patients[17,18]. The critical importance of glutathione was demonstrated by a study which documented significantly decreased erythrocyte glutathione in septic non-survivors *vs* survivors ($P < 0.0001$)[19]. This suggests high levels of circulating H_2O_2 capable of permeating erythrocyte cell membranes and oxidizing (and depleting) intracellular glutathione in septic shock non-survivors. Elegant studies have also demonstrated a significantly higher mitochondrial respiratory rate in non-survivors at three months following sepsis suggesting that failure to down regulate the hypermetabolic state (and excess H_2O_2 production) is independently associated with higher mortality even after surviving the initial infectious insult[20].

Generalized depletion of body stores can result in cellular deficiency of GSH leading to a toxic accumulation of H_2O_2. A highly toxic oxidizing agent, H_2O_2 is the principal mediator of cellular oxidative damage. It does so by generating hydroxyl radical (OH*), the most

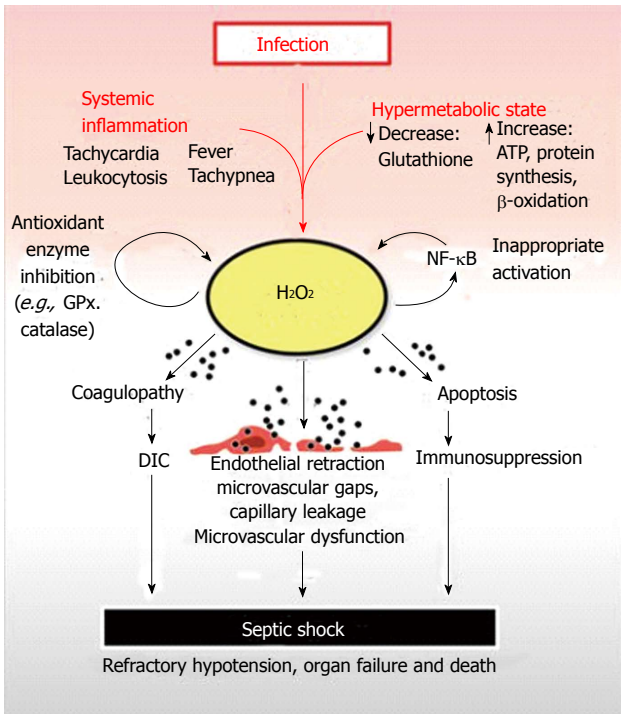


Figure 1 Septic shock begins with a systemic inflammatory reaction to an infection. A contemporaneous increase in metabolism is initiated, which can deplete reserves of critical nutrients such as glutathione. Glutathione is crucial for the neutralization of H_2O_2, a toxic, membrane-permeable oxidizing agent generated as a by-product of cellular metabolism. Depletion of cellular glutathione results in elevation of H_2O_2 which can diffuse out of organ parenchymal cells and into capillary endothelium before reaching the bloodstream. Once in the systemic circulation, excess H_2O_2 is distributed throughout the body resulting in systemic oxidative damage to plasma components, organs and blood vessels. The net result is H_2O_2 induced coagulopathy, immunocyte apoptosis and microvascular dysfunction leading to disseminated intravascular coagulation, immunosuppression, organ failure and septic shock respectively. H_2O_2 inhibits GPx and catalase, which are critical anti-oxidant enzymes required for H_2O_2 neutralization. This prevents restoration of normal plasma and tissue redox balance while exacerbating oxidative tissue damage. H_2O_2 can also activate nuclear factor-κB (NF-κB) contributing to the inappropriate activation of this master pro-inflammatory transcription factor observed in septic shock. The pathologic activation of NF-kB contributes to elevated tumor necrosis factor-alpha levels, another potent generator of intracellular H_2O_2. GPx: Glutathione peroxidase.

potent reactive oxygen radical known in biological systems. Hydroxyl radical will indiscriminately disintegrate proteins, peroxidize lipids and oxidatively damage DNA leading to cell death[21,22].

Compounding the cellular cytotoxicity of H_2O_2 is its ability to freely diffuse through biological membranes allowing it to permeate other cellular compartments and diffuse to the extracellular space from where it can pass through the capillary endothelium into the blood stream[16,23]. Thus, the end result of a systemic GSH deficiency is the systematic discharge of excess H_2O_2 by all organs of the body into the bloodstream where it can damage distant capillary beds leading to systemic microcirculatory dysfunction, microangiopathic edema and refractory hypotension, a hallmark of septic shock.

This is supported by studies showing decreased human endothelial cell levels of GSH and eventual death after *in vitro* exposure to plasma from septic shock patients[24]. This implies a membrane diffusible agent capable of oxidizing intracellular GSH suggesting that a toxic level of plasma H_2O_2 was the offending oxidizing agent mediating this effect. This is consistent with the well documented oxidative damage and dose dependent cytotoxicity that occurs during human endothelial cell exposure to H_2O_2[25,26].

In other studies high levels of urinary H_2O_2 were found to correlate with a fatal outcome in patients with sepsis and adult respiratory distress syndrome suggesting an important role for H_2O_2 in the pathogenesis of septic shock[27]. Taken together the evidence suggests that H_2O_2 exerts a significant microangiopathic effect contributing to the development of microcirculatory dysfunction and the progression to refractory hypotension and fatal septic shock.

MECHANISM OF DISEASE

The above evidence supports a pathogenesis of septic shock which is initiated by the systemic depletion of glutathione as the crucial event responsible for the accumulation of H_2O_2 in tissues. Subsequent diffusion of H_2O_2 into the blood stream leads to systemic elevation of this highly toxic oxidizing agent resulting in the microvascular dysfunction and organ failure observed in septic shock (Figure 1).

At the onset, a systemic inflammatory response is accompanied by a generalized hypermetabolic state which provides the energy needed to sustain the highly upregulated immune response switched on by the presence of a pathogen. The abrupt global increase of cellular bioenergetic reactions to several times their normal basal state presents the cell with a surge of toxic metabolic by-products that must be neutralized to avoid accumulation and cell death. Hydrogen peroxide, a toxic reactive oxygen species, is a significant metabolic by-product that is generated in increased amounts when cellular processes such as protein synthesis, DNA recycling and ATP production are upregulated during periods of hypermetabolism that accompany systemic inflammation.

The majority of cellular H_2O_2 is neutralized by GPx, a selenium containing enzyme, which utilizes the tripeptide co-factor glutathione as a donor of reducing equivalents during the enzymatic conversion of H_2O_2 to water. GSH is consumed in this reaction and must be replenished in order to prevent accumulation of H_2O_2 within the cell. However, during periods of high H_2O_2 production the availability of glutathione may be insufficient to keep up with demand leading to net H_2O_2 accumulation and glutathione depletion resulting in severe cellular dysfunction and organ failure.

Excess H_2O_2 can easily diffuse out of pericapillary parenchymal cells through capillary endothelium and into the blood stream. This augments endothelial generated H_2O_2 resulting in oxidative damage and microangiopathic dysfunction. The inability to buffer cellular H_2O_2 signals a systemic failure of reductive (anti-oxidant)

capacity as the excess oxidant load is discharged into the blood stream. Over time plasma reductive capacity is exhausted leading to severe disruption in plasma redox potential, which studies have shown is strongly associated with an unfavorable outcome[28].

HYDROGEN PEROXIDE CAN REPRODUCE CLINICAL ABNORMALITIES OBSERVED IN SEPTIC SHOCK

Microcirculatory dysfunction

The capillary bed is not simply a conduit for the passage of cells. It is a highly dynamic and integrated system of endothelial cells that continuously interacts with its surrounding environment through a variety of displayed receptors and elaborated mediators whose functions includes vasoregulation, coagulation factors, barrier maintenance, immune cell recruitment and oxygen transport[29]. Microcirculatory dysfunction is now considered to play a central role in the pathogenesis of sepsis and microvascular leakage has a defining role in its outcome[1,29].

Histological analysis of microvasculature in a baboon model of lethal *Escherichia coli* (*E. coli*) sepsis revealed large gaps between endothelial cells accompanied by a significant increase in endothelial permeability[30,31]. These changes are also observed upon exposure of human umbilical vein endothelial cells (HUVEC) to H_2O_2. Studies have demonstrated an 18x increase (from 20 to 360 gaps/mm^2) in inter-endothelial cell gaps within 30 min of HUVEC exposure to H_2O_2. A time and dose dependent H_2O_2 induced endothelial contraction to about 60% of normal planar surface area was also observed[32,33]. This provides a microanatomical basis by which excess H_2O_2 can account for the life threatening massive edema observed both in humans and experimental models of sepsis[29,30].

Accompanying endothelial cell retraction during H_2O_2 exposure is the loss of tight junction proteins at the sites of gap formation, which strongly correlated with increased paracellular permeability[34-36]. Extensive cytoskeletal disruption and rearrangement was also shown to occur after endothelial cell exposure to H_2O_2[37-39]. Endothelial shape changes have been observed to occur in experimental models of sepsis and several studies have reported these pathological changes upon endothelial cell exposure to H_2O_2[30,40-43].

The net effect of continuous H_2O_2 exposure on the systemic microvasculature is severe disruption. Barrier function is compromised, intercellular communication is blunted and signal transduction is abrogated. This leads to microvascular edema, arteriovenous shunts and vasodysregulation as a result of cumulative oxidative damage sustained from continued penetration of H_2O_2 into endothelial cells. This is supported by studies of low dose H_2O_2 perfusion into isolated rat lung, which increased pulmonary vascular bed permeability and capillary filtration coefficient[41].

Studies of bovine brain microvascular endothelial cells exposed to H_2O_2 revealed increased paracellular permeability of the blood brain barrier (BBB) with loss of tight junctional proteins (44)[44]. H_2O_2 can by-pass the normally protective BBB by simply diffusing into tissues and cells[15]. This can result in dysfunction of cerebral microvasculature and could account for the early mental changes observed in patients with sepsis as a result of impaired synaptic transmission[8].

Immune activation

Numerous genes are activated during a systemic immune response in a critically ill or septic individual. Studies in healthy human volunteers receiving low dose endotoxin identified over 4500 activated genes, most of which were involved in the innate or adaptive immune response (5)[5]. The simultaneous activation of this many genes is facilitated by preformed cytoplasmic signal transcription factors that serve as rapid response mediators to injury and infection. Nuclear factor kappa B (NF-κB) is a transcription factor that plays a central role in the activation and regulation of multiple genes that control immune and inflammatory reactions[45]. NF-κB is significantly elevated in adults and children with sepsis[46-48]. NF-κB is also a highly redox sensitive transcription factor capable of being activated by low levels of H_2O_2[49,50] and has been proposed as a biomarker for oxidative stress[51]. This suggests that high levels of ambient H_2O_2 may be involved in the inappropriate activation of NF-κB observed in septic shock[45].

A central role for the innate immune system is suggested by the neutrophilic infiltration into multiple organs observed in septic shock[45]. H_2O_2 is a highly potent neutrophilic chemo-attractant that can establish a chemotactic gradient as it diffuses out of parenchymal cells into the adjacent microvasculature. Circulating neutrophils can track this H_2O_2 gradient and enter the organ parenchyma *via* diapedesis. The net result is neutrophil infiltration into the parenchyma of multiple organs[52-54].

Coagulopathy

Intravascular activation of the coagulation cascade with generation of fibrin and formation of diffuse microvascular thrombi is a pathologic and physiologic hallmark of sepsis[55]. This presents clinically as disseminated intravascular coagulation (DIC) and is found in up to 50% of patients with sepsis[56]. DIC leads to abnormal bleeding and intravascular clotting, obstructing limb and organ blood flow, and is a strong predictor of mortality[56].

Endothelial derived tissue factor (TF) is the major physiological route by which fibrin generation is initiated in sepsis. Importantly, this process is triggered only at sites of vascular injury or endothelial disruption where plasma clotting factors can encounter the TF protein that activates this extrinsic clotting pathway[56,57]. Studies utilizing immunohistochemistry in a lethal *E. coli* baboon sepsis model preferentially localized TF and TF mRNA at arterial branch areas, which is compatible with enhanced contact by a plasma derived oxidizing agent (*e.g.*, H_2O_2) at these sites of altered blood flow[30].

H_2O_2 can induce vascular injury by peroxidation of cell membrane lipids and studies have shown a marked increase in endothelial cell TF and TF mRNA after 1 and 5 min exposure to Xanthine oxidase, a H_2O_2 generating enzyme[10,58]. This indicates that TF is highly sensitive to H_2O_2 induced upregulation, which suggests with a contributory role for H_2O_2 in sepsis- associated DIC. Consistent with this mechanism is a case report describing a fatal case of sepsis with DIC and multiorgan failure in a previously healthy 37-year-old man after receiving several intravenous infusions of H_2O_2[59].

Immunosuppression

Septic patients experience a considerable decline in lymphocyte numbers through apoptosis in the latter stages of sepsis and this is a significant contributing factor to the immunosuppression experienced by septic individuals[60]. Studies have shown that H_2O_2 is a potent apoptosis inducing agent[61]. B lymphocytes treated with agents that inhibit GSH synthesis experience a 95% decline in GSH concentration in 12 h. This is followed by a rise in intracellular H_2O_2 after which apoptosis occurs. By 72 h nearly 50% of B cells have died *via* apoptosis[62]. T cells are also highly sensitive to the effects of GSH depletion. Studies have recorded a 30% decline in circulating T lymphocytes within 4 wk after glutathione levels declined to suboptimal levels in healthy volunteers[63]. This supports a role for H_2O_2 in the development of sepsis induced immunosuppression.

Erythrocyte rigidity

Red blood cell deformability is markedly reduced in sepsis and studies have demonstrated a significant reduction in red blood cell deformability upon exposure to H_2O_2[64]. A direct relationship was found between oxidant induced changes in erythrocyte deformability and severity of multi-organ failure in septic individuals[65]. This suggests that plasma derived H_2O_2 is a source of oxidant-induced RBC membrane damage.

Circulating endothelial cells

Circulating endothelial cells (CEC) are a reliable, sensitive and specific indicator of vascular damage[66]. These cells rarely exist in the peripheral blood of healthy individuals[67]. Patients with s evere sepsis and septic shock have significantly higher numbers of CECs indicating widespread vascular damage[68,69]. Studies have shown that human endothelial cell detachment is produced by exposure to H_2O_2[43]. The presence of CECs in patients with sepsis but without shock suggests that endothelial damage precedes the development of organ damage[68]. This is compatible with H_2O_2 release from organ parenchymal cells into the capillary vascular bed causing microvascular dysfunction and edema with subsequent development of organ failure.

Sepsis associated encephalopathy

Sepsis associated encephalopathy (SAE) is a diffuse cerebral dysfunction occurring in the setting of sepsis but without direct infection of the central nervous system[70]. SAE is characterized by alterations in mental status and motor activity that can range from inattention, disorientation and delirium to agitation, hypoactivity and coma[71,72]. Delirium is frequently the first manifestation of sepsis and often precedes organ failure[73,74]. SAE is reported to occur in up to 70% of septic patients (71).

Neurons are especially sensitive to H_2O_2 induced oxidative damage. Studies have shown a concentration dependent cell death starting at 10 μmol/L when neurons are exposed to H_2O_2[75]. The tripeptide glutathione is critically important in order to prevent oxidative damage of the brain due to H_2O_2[76]. Glutathione is composed of amino acids glycine, cysteine and glutamate. Cysteine is the rate limiting substrate for neuronal glutathione synthesis and transsulfuration of homocysteine is a major source of cysteine in most cells. However, the brain' s neuronal transsulfuration pathway is thought to be a negligible source of cysteine due to low activity of neuronal cystathionine-gamma-lyase (EC 4.4.1.1), a crucial enzyme in the transsulfurationn pathway leading to the synthesis of cysteine[77,78]. Neurons, therefore, rely mainly on the absorption of extracellular cysteine provided by astrocytes for the synthesis of glutathione[77]. Thus, the dependence of brain neurons on extracellular cysteine in order to synthesize glutathione severely limits their ability to upregulate antioxidant defenses in response to H_2O_2 mediated oxidative stress. This makes brain neurons highly vulnerable to H_2O_2 oxidative damage and dysfunction. This is consistent with the encephalopathy that is reported to occur after accidental ingestion of H_2O_2[79]. Encephalopathy was also a manifestation after intravenous administration of H_2O_2 during alternative medicine therapy[59].

The main interaction site of neurons and astrocytes is the synaptic cleft[80]. Astrocytes export glutathione directly into the synaptic cleft. Ectoenzymes present in the synapse enzymatically release cysteine from glutathione after which cysteine is transported into neurons by the membrane bound EAAT3 transporter (excitatory amino acid transporter 3)[77-82]. H_2O_2 can react non-enzymatically with cysteine in the synaptic cleft to produce cystine[83]. This removes cysteine from the synapse and prevents its importation into the neuron resulting in oxidative stress by decreasing the synthesis of neuronal glutathione. The presence of thiols (*i.e.*, cysteine) in the synaptic cleft suggests that this region can function as a sink for H_2O_2 resulting in disruption of synaptic transmission as a result of peroxidation of synaptic cellular membranes.

Thus, circulating H_2O_2 can permeate the brain during the initial hypermetabolic systemic inflammatory response syndrome (SIRS) phase of sepsis and disrupt brain function in the early stages of disease. Due to their limited capacity to detoxify H_2O_2, brain neurons are the first cells to be affected by H_2O_2 induced oxidative stress[84]. This is consistent with the observation that encephalopathy is often the first sign of sepsis.

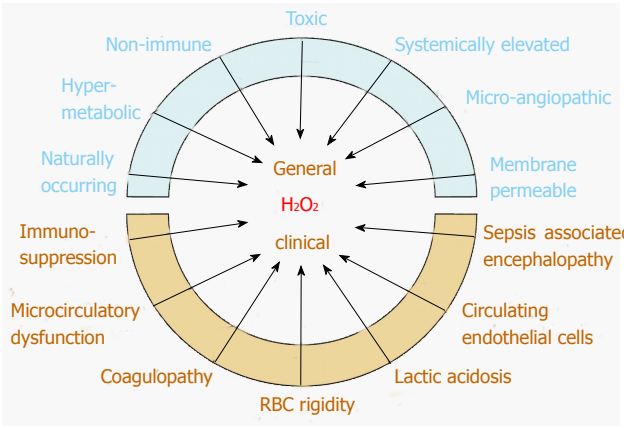


Figure 2 Pathologically elevated serum H_2O_2 levels can account for the general physiological, histological and clinical abnormalities observed in septic shock. Red blood cell glutathione accounts for a major portion of serum redox buffering capacity and is depleted in septic shock non-survivors vs. survivors. Brain neuron function is highly vulnerable to H_2O_2 oxidative stress and is manifested by electroencephalographic changes, which can appear before clinical encephalopathy is evident. Studies show that septic shock survivors upregulate serum antioxidant capacity (which decreases H_2O_2), while non-survivors are unable to do so. This suggests that elevated H_2O_2 is a necessary concomitant to the development of septic shock and recovery is preceded by decreasing H_2O_2. The individual clinical course, bookended by these extremes of H_2O_2, is influenced by parameters such as individual antioxidant capacity, susceptibility to oxidative stress, co-morbidities, age, general health and organ system involved.

LACTIC ACIDOSIS

Sepsis related lactic acidosis is generally attributed to tissue hypoxia. Although tissue hypoxia can result in lactic acidosis it is unsuitable as a general mechanism to explain the appearance of lactic acidosis in septic patients when tissue oxygenation can be normal or even increased[85].

Under normal circumstances pyruvate, the end product of glycolysis in the cytoplasm, is transported into mitochondria where it is oxidized by the Krebs cycle. Lactate synthesis increases when the rate of pyruvate formation in the cytoplasm exceeds its rate of oxidation by the mitochondria. The excess pyruvate in the cytoplasm is then converted to lactate by lactate dehydrogenase and released into the blood stream resulting in lactic acidosis.

Inhibition of Krebs cycle enzymes will decrease pyruvate oxidation resulting in lactic acidosis. This has been observed with inherited deficiency of alpha-ketoglutarate dehydrogenase resulting in severe congenital lactic acidosis[86]. Alpha-ketoglutarate dehydrogenase is also highly sensitive to oxidative inhibition by hydrogen peroxide[87]. Rising systemic concentrations of H_2O_2 in sepsis can account for the observed lactic acidosis with normal tissue oxygen perfusion. This has been termed cytopathic hypoxia. In this case the lactic acidosis is an epiphenomenon of a much more serious underlying metabolic abnormality and treatment of the acidosis does not resolve the inhibition of the Krebs cycle.

DISCUSSION

A hypermetabolic state can develop very quickly after a generalized septic or non-septic insult to the body. At the heart of the hypermetabolic state is a significantly increased bioenergetic response resulting mainly from enhanced ETC activity. The ETC is an assembly of intramitochondrial protein complexes that converts the energy of high-energy electrons into a form that is used to synthesize ATP, a high energy molecule that powers most energy requiring biosynthetic reactions and physiological functions. Thus, the high energy demands of body systems resulting from a generalized septic or non-septic insult are principally met by increased ATP production, which is manifested as a hypermetabolic state and recognized by the same parameters used to define a SIRS such as increased body temperature, heart rate, respiratory rate and increased white blood cell count.

A principle metabolic by-product of ETC activity is hydrogen peroxide; a highly toxic oxidizing agent. Hydrogen peroxide is produced when electrons spontaneously escape from the ETC and combine with available vicinal oxygen to generate superoxide that is enzymatically converted to H_2O_2 by superoxide dismutase. The increased amount of H_2O_2 generated during a hypermetabolic state can overwhelm the cell's anti-oxidant enzymatic defenses resulting in net intracellular H_2O_2 accumulation. The excess H_2O_2 can oxidatively inhibit enzyme systems including those needed to neutralize H_2O_2 resulting in a positive bio-feedback loop and a vicious cycle of ever increasing intracellular H_2O_2[88]. Glutathione functions as a cofactor for GPx, which enzymatically neutralizes H_2O_2. GPx is inhibited by the rising concentrations of H_2O_2, which explains why exogenously supplied N-acetylcysteine has no effect on the course of septic shock since glutathione cannot be utilized by GPx to neutralize H_2O_2[88,89].

Hydrogen peroxide is biomembrane permeable and can diffuse into the bloodstream where it is distributed to all organs of the body generating a state of severe systemic oxidative stress. Studies have documented high levels of H_2O_2 in the blood and urine of septic patients[27,90]. This can result in the multi-organ failure and microangiopathic dysfunction characteristic of septic shock. Genetic variation in glutathione levels as well as age related decline has been reported[91-93]. This may compromise the ability to neutralize H_2O_2 and predispose individuals to vasoplegic (*i.e.*, septic) shock and multi-organ failure during acute hypermetabolic periods, especially in older individuals. Studies have shown that glutathione is essential for cell survival[94].

CONCLUSION

Taken together, the evidence suggests that septic shock is a primary radical induction process that has its origins early in the development of sepsis with the accumulation and generalized dispersal of cytotoxic levels of H_2O_2. This arises secondary to glutathione depletion as a result of a systemic inflammatory mediated hypermetabolic state. Studies have shown that systemic inflammation significantly reduces GSH levels, and GSH deficient animals

subjected to shock develop hypotension, kidney and liver failure, increased organ bacteria and dramatic increases in mortality rates[95-97].

The near universal requirement of glutathione for cellular function and the pathological accumulation of H_2O_2 that ensues when glutathione is deficient can affect every organ in the body. Studies have shown that H_2O_2 can reproduce the clinico-pathological abnormalities observed in septic shock (Figure 2).

Kept in check, the high membrane diffusability of H_2O_2 allows it to fulfill its physiological role as a cellular messenger but also creates the potential for a pathophysiological response during times of metabolic stress when reductive (anti-oxidant) mechanisms can become overwhelmed as a consequence of hyper-metabolic H_2O_2 production[98]. This is further exacerbated by nutritional deficits that may arise during the course of acute illness in addition to the effect of glutathione deficiency itself, which as master antioxidant of the cell, supplies reducing equivalents to maintain proteins in their reduced (and functional) state[14].

REFERENCES

1 **Goldenberg NM**, Steinberg BE, Slutsky AS, Lee WL. Broken barriers: a new take on sepsis pathogenesis. *Sci Transl Med* 2011; **3**: 88ps25 [PMID: 21697528 DOI: 10.1126/scitranslmed.3002011]

2 **Marshall JC**, Vincent JL, Guyatt G, Angus DC, Abraham E, Bernard G, Bombardier C, Calandra T, Jørgensen HS, Sylvester R, Boers M. Outcome measures for clinical research in sepsis: a report of the 2nd Cambridge Colloquium of the International Sepsis Forum. *Crit Care Med* 2005; **33**: 1708-1716 [PMID: 16096445 DOI: 10.1097/01.CCM.0000174478.70338.03]

3 **Melamed A**, Sorvillo FJ. The burden of sepsis-associated mortality in the United States from 1999 to 2005: an analysis of multiple-cause-of-death data. *Crit Care* 2009; **13**: R28 [PMID: 19250547 DOI: 10.1186/cc7733]

4 **American Cancer Society, Surveillance Research**. Estimated New Cancer Cases and Deaths by Sex for All Sites, US, 2011. Available from: URL: http://seer.cancer.gov/csr/1975_2008/results_single/sect_01_table.01.pdfAccessed 20/Jan/2014

5 **Xiao W**, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Brownstein BH, Mason PH, Baker HV, Finnerty CC, Jeschke MG, López MC, Klein MB, Gamelli RL, Gibran NS, Arnoldo B, Xu W, Zhang Y, Calvano SE, McDonald-Smith GP, Schoenfeld DA, Storey JD, Cobb JP, Warren HS, Moldawer LL, Herndon DN, Lowry SF, Maier RV, Davis RW, Tompkins RG. A genomic storm in critically injured humans. *J Exp Med* 2011; **208**: 2581-2590 [PMID: 22110166 DOI: 10.1084/jem.20111354]

6 **Suffredini AF**, Munford RS. Novel therapies for septic shock over the past 4 decades. *JAMA* 2011; **306**: 194-199 [PMID: 21750297 DOI: 10.1001/jama.2011.909]

7 **Bloch KC**. Infectious Diseases. In: McPhee SJ, Hammer GD: Pathophysiology of Disease. New York: McGraw-Hill, 2010: 57-83

8 **Borgen L**. Total parenteral nutrition in adults. *Am J Nurs* 1978; **78**: 224-228 [PMID: 417629 DOI: 10.2307/3424283]

9 **Depuydt M**, Messens J, Collet JF. How proteins form disulfide bonds. *Antioxid Redox Signal* 2011; **15**: 49-66 [PMID: 20849374 DOI: 10.1089/ars.2010.3575]

10 **Kelley EE**, Khoo NK, Hundley NJ, Malik UZ, Freeman BA, Tarpey MM. Hydrogen peroxide is the major oxidant product of xanthine oxidase. *Free Radic Biol Med* 2010; **48**: 493-498 [PMID: 19941951 DOI: 10.1016/j.freeradbiomed.2009.11.012]

11 **Murphy MP**. How mitochondria produce reactive oxygen species. *Biochem J* 2009; **417**: 1-13 [PMID: 19061483 DOI: 10.1042/BJ20081386]

12 **Schrader M**, Fahimi HD. Mammalian peroxisomes and reactive oxygen species. *Histochem Cell Biol* 2004; **122**: 383-393 [PMID: 15241609 DOI: 10.1007/s00418-004-0673-1]

13 **Forman HJ**, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. *Mol Aspects Med* 2009; **30**: 1-12 [PMID: 18796312 DOI: 10.1016/j.mam.2008.08.006]

14 **Wu G**, Fang YZ, Yang S, Lupton JR, Turner ND. Glutathione metabolism and its implications for health. *J Nutr* 2004; **134**: 489-492 [PMID: 14988435]

15 **Lyons J**, Rauh-Pfeiffer A, Ming-Yu Y, Lu XM, Zurakowski D, Curley M, Collier S, Duggan C, Nurko S, Thompson J, Ajami A, Borgonha S, Young VR, Castillo L. Cysteine metabolism and whole blood glutathione synthesis in septic pediatric patients. *Crit Care Med* 2001; **29**: 870-877 [PMID: 11373484 DOI: 10.1097/00003246-200104000-00036]

16 **Biolo G**, Antonione R, De Cicco M. Glutathione metabolism in sepsis. *Crit Care Med* 2007; **35**: S591-S595 [PMID: 17713414 DOI: 10.1097/01.CCM.0000278913.19123.13]

17 **Pacht ER**, Timerman AP, Lykens MG, Merola AJ. Deficiency of alveolar fluid glutathione in patients with sepsis and the adult respiratory distress syndrome. *Chest* 1991; **100**: 1397-1403 [PMID: 1935300 DOI: 10.1378/chest.100.5.1397]

18 **Hammarqvist F**, Luo JL, Cotgreave IA, Andersson K, Wernerman J. Skeletal muscle glutathione is depleted in critically ill patients. *Crit Care Med* 1997; **25**: 78-84 [PMID: 8989180 DOI: 10.1097/00003246-199701000-00016]

19 **Karapetsa M**, Pitsika M, Goutzourelas N, Stagos D, Tousia Becker A, Zakynthinos E. Oxidative status in ICU patients with septic shock. *Food Chem Toxicol* 2013; **61**: 106-111 [PMID: 23542126 DOI: 10.1016/j.fct.2013.03.026]

20 **Sjövall F**, Morota S, Hansson MJ, Friberg H, Gnaiger E, Elmér E. Temporal increase of platelet mitochondrial respiration is negatively associated with clinical outcome in patients with sepsis. *Crit Care* 2010; **14**: R214 [PMID: 21106065 DOI: 10.1186/cc9337]

21 **Shokolenko I**, Venediktova N, Bochkareva A, Wilson GL, Alexeyev MF. Oxidative stress induces degradation of mitochondrial DNA. *Nucleic Acids Res* 2009; **37**: 2539-2548 [PMID: 19264794 DOI: 10.1093/nar/gkp100]

22 **Van Houten B**, Woshner V, Santos JH. Role of mitochondrial DNA in toxic responses to oxidative stress. *DNA Repair* (Amst) 2006; **5**: 145-152 [PMID: 15878696 DOI: 10.1016/j.dnarep.2005.03.002]

23 **Malinouski M**, Zhou Y, Belousov VV, Hatfield DL, Gladyshev VN. Hydrogen peroxide probes directed to different cellular compartments. *PLoS One* 2011; **6**: e14564 [PMID: 21283738 DOI: 10.1371/journal.pone.0014564]

24 **Huet O**, Cherreau C, Nicco C, Dupic L, Conti M, Borderie D, Pene F, Vicaut E, Benhamou D, Mira JP, Duranteau J, Batteux F. Pivotal role of glutathione depletion in plasma-induced endothelial oxidative stress during sepsis. *Crit Care Med* 2008; **36**: 2328-2334 [PMID: 18664787 DOI: 10.1097/CCM.0b013e3181800387]

25 **Chen J**, Gu Y, Shao Z, Luo J, Tan Z. Propofol protects against hydrogen peroxide-induced oxidative stress and cell dysfunction in human umbilical vein endothelial cells. *Mol Cell Biochem* 2010; **339**: 43-54 [PMID: 20039104 DOI: 10.1007/s11010-009-0368-y]

26 **Li ZL**, Liu JC, Hu J, Li XQ, Wang SW, Yi DH, Zhao MG. Protective effects of hyperoside against human umbilical vein endothelial cell damage induced by hydrogen peroxide.

J Ethnopharmacol 2012; **139**: 388-394 [PMID: 22120016 DOI: 10.1016/j.jep.2011.11.020]
27 **Mathru M**, Rooney MW, Dries DJ, Hirsch LJ, Barnes L, Tobin MJ. Urine hydrogen peroxide during adult respiratory distress syndrome in patients with and without sepsis. *Chest* 1994; **105**: 232-236 [PMID: 8275738 DOI: 10.1378/chest.105.1.232]
28 **Cowley HC**, Bacon PJ, Goode HF, Webster NR, Jones JG, Menon DK. Plasma antioxidant potential in severe sepsis: a comparison of survivors and nonsurvivors. *Crit Care Med* 1996; **24**: 1179-1183 [PMID: 8674332 DOI: 10.1097/00003246-199607000-00019]
29 **Lehr HA**, Bittinger F, Kirkpatrick CJ. Microcirculatory dysfunction in sepsis: a pathogenetic basis for therapy? *J Pathol* 2000; **190**: 373-386 [PMID: 10685071]
30 **Lupu C**, Westmuckett AD, Peer G, Ivanciu L, Zhu H, Taylor FB, Lupu F. Tissue factor-dependent coagulation is preferentially up-regulated within arterial branching areas in a baboon model of Escherichia coli sepsis. *Am J Pathol* 2005; **167**: 1161-1172 [PMID: 16192650 DOI: 10.1016/S0002-9440(10)61204-7]
31 **Birukova AA**, Arce FT, Moldobaeva N, Dudek SM, Garcia JG, Lal R, Birukov KG. Endothelial permeability is controlled by spatially defined cytoskeletal mechanics: atomic force microscopy force mapping of pulmonary endothelial monolayer. *Nanomedicine* 2009; **5**: 30-41 [PMID: 18824415 DOI: 10.1016/j.nano.2008.07.002]
32 **Hastie LE**, Patton WF, Hechtman HB, Shepro D. H2O2-induced filamin redistribution in endothelial cells is modulated by the cyclic AMP-dependent protein kinase pathway. *J Cell Physiol* 1997; **172**: 373-381 [PMID: 9284957]
33 **López-Ongil S**, Torrecillas G, Pérez-Sala D, González-Santiago L, Rodríguez-Puyol M, Rodríguez-Puyol D. Mechanisms involved in the contraction of endothelial cells by hydrogen peroxide. *Free Radic Biol Med* 1999; **26**: 501-510 [PMID: 10218638 DOI: 10.1016/S0891-5849(98)00223-8]
34 **Kevil CG**, Okayama N, Alexander JS. H(2)O(2)-mediated permeability II: importance of tyrosine phosphatase and kinase activity. *Am J Physiol Cell Physiol* 2001; **281**: C1940-C1947 [PMID: 11698252]
35 **Kevil CG**, Oshima T, Alexander B, Coe LL, Alexander JS. H(2)O(2)-mediated permeability: role of MAPK and occludin. *Am J Physiol Cell Physiol* 2000; **279**: C21-C30 [PMID: 10898713]
36 **Pearse DB**, Shimoda LA, Verin AD, Bogatcheva N, Moon C, Ronnett GV, Welsh LE, Becker PM. Effect of cGMP on lung microvascular endothelial barrier dysfunction following hydrogen peroxide. *Endothelium* 2003; **10**: 309-317 [PMID: 14741846 DOI: 10.1080/714007541]
37 **Valen G**, Sondén A, Vaage J, Malm E, Kjellström BT. Hydrogen peroxide induces endothelial cell atypia and cytoskeleton depolymerization. *Free Radic Biol Med* 1999; **26**: 1480-1488 [PMID: 10401612 DOI: 10.1016/S0891-5849(99)00009-X]
38 **Bradley JR**, Thiru S, Pober JS. Hydrogen peroxide-induced endothelial retraction is accompanied by a loss of the normal spatial organization of endothelial cell adhesion molecules. *Am J Pathol* 1995; **147**: 627-641 [PMID: 7677177]
39 **Zhao Y**, Davis HW. Hydrogen peroxide-induced cytoskeletal rearrangement in cultured pulmonary endothelial cells. *J Cell Physiol* 1998; **174**: 370-379 [PMID: 9462699 DOI: 10.1002/(SICI)1097-4652(199803)174]
40 **Hirano S**, Rees RS, Yancy SL, Welsh MJ, Remick DG, Yamada T, Hata J, Gilmont RR. Endothelial barrier dysfunction caused by LPS correlates with phosphorylation of HSP27 in vivo. *Cell Biol Toxicol* 2004; **20**: 1-14 [PMID: 15119843]
41 **Habib MP**, Clements NC. Effects of low-dose hydrogen peroxide in the isolated perfused rat lung. *Exp Lung Res* 1995; **21**: 95-112 [PMID: 7729381 DOI: 10.3109/01902149509031747]
42 **Gilmont RR**, Dardano A, Young M, Engle JS, Adamson BS, Smith DJ, Rees RS. Effects of glutathione depletion on oxidant-induced endothelial cell injury. *J Surg Res* 1998; **80**: 62-68 [PMID: 9790816 DOI: 10.1006/jsre.1998.5328]
43 **Shingu M**, Yoshioka K, Nobunaga M, Yoshida K. Human vascular smooth muscle cells and endothelial cells lack catalase activity and are susceptible to hydrogen peroxide. *Inflammation* 1985; **9**: 309-320 [PMID: 4044027 DOI: 10.1007/BF00916279]
44 **Lee HS**, Namkoong K, Kim DH, Kim KJ, Cheong YH, Kim SS, Lee WB, Kim KY. Hydrogen peroxide-induced alterations of tight junction proteins in bovine brain microvascular endothelial cells. *Microvasc Res* 2004; **68**: 231-238 [PMID: 15501242 DOI: 10.1016/j.mvr.2004.07.005]
45 **Liu SF**, Malik AB. NF-kappa B activation as a pathological mechanism of septic shock and inflammation. *Am J Physiol Lung Cell Mol Physiol* 2006; **290**: L622-L645 [PMID: 16531564 DOI: 10.1152/ajplung.00477.2005]
46 **Arnalich F**, Garcia-Palomero E, López J, Jiménez M, Madero R, Renart J, Vázquez JJ, Montiel C. Predictive value of nuclear factor kappaB activity and plasma cytokine levels in patients with sepsis. *Infect Immun* 2000; **68**: 1942-1945 [PMID: 10722586 DOI: 10.1128/IAI.68.4.1942-1945.2000]
47 **Böhrer H**, Qiu F, Zimmermann T, Zhang Y, Jllmer T, Männel D, Böttiger BW, Stern DM, Waldherr R, Saeger HD, Ziegler R, Bierhaus A, Martin E, Nawroth PP. Role of NFkappaB in the mortality of sepsis. *J Clin Invest* 1997; **100**: 972-985 [PMID: 9276714 DOI: 10.1172/JCI119648]
48 **Hotta N**, Ichiyama T, Shiraishi M, Takekawa T, Matsubara T, Furukawa S. Nuclear factor-kappaB activation in peripheral blood mononuclear cells in children with sepsis. *Crit Care Med* 2007; **35**: 2395-2401 [PMID: 17944030 DOI: 10.1097/01.CCM.0000284502.38701.E6]
49 **Schreck R**, Albermann K, Baeuerle PA. Nuclear factor kappa B: an oxidative stress-responsive transcription factor of eukaryotic cells (a review). *Free Radic Res Commun* 1992; **17**: 221-237 [PMID: 1473734 DOI: 10.3109/10715769209079515]
50 **Takada Y**, Mukhopadhyay A, Kundu GC, Mahabeleshwar GH, Singh S, Aggarwal BB. Hydrogen peroxide activates NF-kappa B through tyrosine phosphorylation of I kappa B alpha and serine phosphorylation of p65: evidence for the involvement of I kappa B alpha kinase and Syk protein-tyrosine kinase. *J Biol Chem* 2003; **278**: 24233-24241 [PMID: 12711606 DOI: 10.1074/jbc.M212389200]
51 **van den Berg R**, Haenen GR, van den Berg H, Bast A. Transcription factor NF-kappaB as a potential biomarker for oxidative stress. *Br J Nutr* 2001; **86** Suppl 1: S121-S127 [PMID: 11520430 DOI: 10.1079/BJN2001340]
52 **Niethammer P**, Grabher C, Look AT, Mitchison TJ. A tissue-scale gradient of hydrogen peroxide mediates rapid wound detection in zebrafish. *Nature* 2009; **459**: 996-999 [PMID: 19494811 DOI: 10.1038/nature08119]
53 **Klyubin IV**, Kirpichnikova KM, Gamaley IA. Hydrogen peroxide-induced chemotaxis of mouse peritoneal neutrophils. *Eur J Cell Biol* 1996; **70**: 347-351 [PMID: 8864663]
54 **Mathias JR**, Perrin BJ, Liu TX, Kanki J, Look AT, Huttenlocher A. Resolution of inflammation by retrograde chemotaxis of neutrophils in transgenic zebrafish. *J Leukoc Biol* 2006; **80**: 1281-1288 [PMID: 16963624 DOI: 10.1189/jlb.0506346]
55 **Wang L**, Bastarache JA, Ware LB. The coagulation cascade in sepsis. *Curr Pharm Des* 2008; **14**: 1860-1869 [PMID: 18691097 DOI: 10.2174/138161208784980581]
56 **Zeerleder S**, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. *Chest* 2005; **128**: 2864-2875 [PMID: 16236964 DOI: 10.1378/chest.128.4.2864]
57 **Crawley JT**, Lane DA. The haemostatic role of tissue factor pathway inhibitor. *Arterioscler Thromb Vasc Biol* 2008; **28**: 233-242 [PMID: 17951326 DOI: 10.1161/ATVBAHA.107.141606]
58 **Ambrosio G**, Tritto I, Golino P. Reactive oxygen metabolites and arterial thrombosis. *Cardiovasc Res* 1997; **34**: 445-452 [PMID: 9231027 DOI: 10.1016/S0008-6363(97)00101-6]

59 **Wetter DA**, Davis MD. Ulceration of the arm attributed to a spider bite and treated with intravenous hydrogen peroxide: a cautionary tale. *Arch Dermatol* 2006; **142**: 1658-1659 [PMID: 17179007 DOI: 10.1001/archderm.142.12.1658]

60 **Stearns-Kurosawa DJ**, Osuchowski MF, Valentine C, Kurosawa S, Remick DG. The pathogenesis of sepsis. *Annu Rev Pathol* 2011; **6**: 19-48 [PMID: 20887193 DOI: 10.1146/annurev-pathol-011110-130327]

61 **Cerella C**, Coppola S, Maresca V, De Nicola M, Radogna F, Ghibelli L. Multiple mechanisms for hydrogen peroxide-induced apoptosis. *Ann N Y Acad Sci* 2009; **1171**: 559-563 [PMID: 19723104 DOI: 10.1111/j.1749-6632.2009.04901.x]

62 **Armstrong JS**, Steinauer KK, Hornung B, Irish JM, Lecane P, Birrell GW, Peehl DM, Knox SJ. Role of glutathione depletion and reactive oxygen species generation in apoptotic signaling in a human B lymphoma cell line. *Cell Death Differ* 2002; **9**: 252-263 [PMID: 11859408 DOI: 10.1038/sj.cdd.4400959]

63 **Kinscherf R**, Fischbach T, Mihm S, Roth S, Hohenhaus-Sievert E, Weiss C, Edler L, Bärtsch P, Dröge W. Effect of glutathione depletion and oral N-acetyl-cysteine treatment on CD4+ and CD8+ cells. *FASEB J* 1994; **8**: 448-451 [PMID: 7909525]

64 **Snyder LM**, Fortier NL, Trainor J, Jacobs J, Leb L, Lubin B, Chiu D, Shohet S, Mohandas N. Effect of hydrogen peroxide exposure on normal human erythrocyte deformability, morphology, surface characteristics, and spectrin-hemoglobin cross-linking. *J Clin Invest* 1985; **76**: 1971-1977 [PMID: 4056060 DOI: 10.1172/JCI112196]

65 **Machiedo GW**, Powell RJ, Rush BF, Swislocki NI, Dikdan G. The incidence of decreased red blood cell deformability in sepsis and the association with oxygen free radical damage and multiple-system organ failure. *Arch Surg* 1989; **124**: 1386-1389 [PMID: 2589962 DOI: 10.1001/archsurg.1989.01410120032007]

66 **Erdbruegger U**, Dhaygude A, Haubitz M, Woywodt A. Circulating endothelial cells: markers and mediators of vascular damage. *Curr Stem Cell Res Ther* 2010; **5**: 294-302 [PMID: 20528750 DOI: 10.2174/157488810793351721]

67 **Wu H**, Chen H, Hu PC. Circulating endothelial cells and endothelial progenitors as surrogate biomarkers in vascular dysfunction. *Clin Lab* 2007; **53**: 285-295 [PMID: 17605403]

68 **Mutunga M**, Fulton B, Bullock R, Batchelor A, Gascoigne A, Gillespie JI, Baudouin SV. Circulating endothelial cells in patients with septic shock. *Am J Respir Crit Care Med* 2001; **163**: 195-200 [PMID: 11208646 DOI: 10.1164/ajrccm.163.1.9912036]

69 **Schlichting DE**, Waxman AB, O'Brien LA, Wang T, Naum CC, Rubeiz GJ, Um SL, Williams M, Yan SC. Circulating endothelial and endothelial progenitor cells in patients with severe sepsis. *Microvasc Res* 2011; **81**: 216-221 [PMID: 21130783 DOI: 10.1016/j.mvr.2010.11.011]

70 **Gofton TE**, Young GB. Sepsis-associated encephalopathy. *Nat Rev Neurol* 2012; **8**: 557-566 [PMID: 22986430 DOI: 10.1038/nrneurol.2012.183]

71 **Lamar CD**, Hurley RA, Taber KH. Sepsis-associated encephalopathy: review of the neuropsychiatric manifestations and cognitive outcome. *J Neuropsychiatry Clin Neurosci* 2011; **23**: 237-241 [PMID: 21948885 DOI: 10.1176/appi.neuropsych.23.3.237]

72 Siami S, Polito A, Sharshar T. Sepsis-associated Encephalopathy. In Vincent JL Yearbook of Intensive Care and Emergency Medicine. Berlin-Heidelberg: Springer, 2009: 809-816

73 **Wilson JX**, Young GB. Progress in clinical neurosciences: sepsis-associated encephalopathy: evolving concepts. *Can J Neurol Sci* 2003; **30**: 98-105 [PMID: 12774948]

74 **Ringer TM**, Axer H, Romeike BF, Zinke J, Brunkhorst F, Witte OW, Günther A. Neurological Sequelae of Sepsis: I) Septic Encephalopathy. *Open Crit Care Med J* 2011; **4**: 2-7 [DOI: 10.2174/1874828701104010002]

75 **Desagher S**, Glowinski J, Premont J. Astrocytes protect neurons from hydrogen peroxide toxicity. *J Neurosci* 1996; **16**: 2553-2562 [PMID: 8786431]

76 **Dringen R**, Pawlowski PG, Hirrlinger J. Peroxide detoxification by brain cells. *J Neurosci Res* 2005; **79**: 157-165 [PMID: 15573410 DOI: 10.1002/jnr.20280]

77 **Aoyama K**, Watabe M, Nakaki T. Regulation of neuronal glutathione synthesis. *J Pharmacol Sci* 2008; **108**: 227-238 [PMID: 19008644 DOI: 10.1254/jphs.08R01CR]

78 **Deth R**, Muratore C. The redox/methylation hypothesis of autism. In: Chauhan A, Chauhan V, Brown WT : Autism: Oxidative Stress, Inflammation and immune abnormalities. Florida: Florida CRC Press, 2010: 113-130

79 **Cannon G**, Caravati EM, Filloux FM. Hydrogen peroxide neurotoxicity in childhood: case report with unique magnetic resonance imaging features. *J Child Neurol* 2003; **18**: 805-808 [PMID: 14696912 DOI: 10.1177/08830738030180111501]

80 **Cakir T**, Alsan S, Saybasili H, Akin A, Ulgen KO. Reconstruction and flux analysis of coupling between metabolic pathways of astrocytes and neurons: application to cerebral hypoxia. *Theor Biol Med Model* 2007; **4**: e48

81 **Wang XF**, Cynader MS. Astrocytes provide cysteine to neurons by releasing glutathione. *J Neurochem* 2000; **74**: 1434-1442 [PMID: 10737599 DOI: 10.1046/j.1471-4159.2000.0741434.x]

82 **Dringen R**, Hirrlinger J. Glutathione pathways in the brain. *Biol Chem* 2003; **384**: 505-516 [PMID: 12751781 DOI: 10.1515/BC.2003.059]

83 **Luo D**, Smith SW, Anderson BD. Kinetics and mechanism of the reaction of cysteine and hydrogen peroxide in aqueous solution. *J Pharm Sci* 2005; **94**: 304-316 [PMID: 15570599 DOI: 10.1002/jps.20253]

84 **Chauhan A**, Chauhan V. Oxidative stress in autism. *Pathophysiology* 2006; **13**: 171-181 [PMID: 16766163 DOI: 10.1201/9781420068870]

85 **Bellomo R**, Ronco C. The pathogenesis of lactic acidosis in sepsis. *Curr Opin Crit Care* 1999; **5**: 452-457 [DOI: 10.1097/00075198-199912000-00008]

86 **Bonnefont JP**, Chretien D, Rustin P, Robinson B, Vassault A, Aupetit J, Charpentier C, Rabier D, Saudubray JM, Munnich A. Alpha-ketoglutarate dehydrogenase deficiency presenting as congenital lactic acidosis. *J Pediatr* 1992; **121**: 255-258 [PMID: 1640293 DOI: 10.1016/S0022-3476(05)81199-0]

87 **Tretter L**, Adam-Vizi V. Inhibition of Krebs cycle enzymes by hydrogen peroxide: A key role of [alpha]-ketoglutarate dehydrogenase in limiting NADH production under oxidative stress. *J Neurosci* 2000; **20**: 8972-8979 [PMID: 11124972]

88 **Cho CS**, Lee S, Lee GT, Woo HA, Choi EJ, Rhee SG. Irreversible inactivation of glutathione peroxidase 1 and reversible inactivation of peroxiredoxin II by H2O2 in red blood cells. *Antioxid Redox Signal* 2010; **12**: 1235-1246 [PMID: 20070187 DOI: 10.1089/ars.2009.2701]

89 **Kinnula VL**, Everitt JI, Mangum JB, Chang LY, Crapo JD. Antioxidant defense mechanisms in cultured pleural mesothelial cells. *Am J Respir Cell Mol Biol* 1992; **7**: 95-103 [PMID: 1627338 DOI: 10.1165/ajrcmb/7.1.95]

90 **Pherwani AV**, Puri VC, V Malhotra V. Estimation of hydrogen peroxide levels in the blood and urine of normal infants and infants with sepsis. *Bombay Hosp J* 1999; **41**: 8

91 **van 't Erve TJ**, Wagner BA, Ryckman KK, Raife TJ, Buettner GR. The concentration of glutathione in human erythrocytes is a heritable trait. *Free Radic Biol Med* 2013; **65**: 742-749 [PMID: 23938402 DOI: 10.1016/j.freeradbiomed.2013.08.002]

92 **Caprari P**, Caforio MP, Cianciulli P, Maffi D, Pasquino MT, Tarzia A, Amadori S, Salvati AM. 6-Phosphogluconate dehydrogenase deficiency in an Italian family. *Ann Hematol* 2001; **80**: 41-44 [PMID: 11233775 DOI: 10.1007/s002770000233]

93 **Lang CA**, Naryshkin S, Schneider DL, Mills BJ, Lindeman RD. Low blood glutathione levels in healthy aging adults. *J Lab Clin Med* 1992; **120**: 720-725 [PMID: 1431500]

94 **Hatem E**, Berthonaud V, Dardalhon M, Lagniel G, Baudouin-Cornu P, Huang ME, Labarre J, Chédin S. Glutathione is essential to preserve nuclear function and cell survival under

oxidative stress. *Free Radic Biol Med* 2014; **67**: 103-114 [PMID: 24145121 DOI: 10.1016/j.freeradbiomed.2013.10.807]

95 **Keller GA**, Barke R, Harty JT, Humphrey E, Simmons RL. Decreased hepatic glutathione levels in septic shock. Predisposition of hepatocytes to oxidative stress: an experimental approach. *Arch Surg* 1985; **120**: 941-945 [PMID: 3893390 DOI: 10.1001/archsurg.1985.01390320065013]

96 **Ikegami K**, Lalonde C, Young YK, Picard L, Demling R. Comparison of plasma reduced glutathione and oxidized glutathione with lung and liver tissue oxidant and antioxidant activity during acute inflammation. *Shock* 1994; **1**: 307-312 [PMID: 7735965 DOI: 10.1097/00024382-199404000-00010]

97 **Robinson MK**, Rounds JD, Hong RW, Jacobs DO, Wilmore DW. Glutathione deficiency increases organ dysfunction after hemorrhagic shock. *Surgery* 1992; **112**: 140-147; discussion 148-149 [PMID: 1641757]

98 **Holmquist L**, Stuchbury G, Steele M, Münch G. Hydrogen peroxide is a true first messenger. *J Neural Transm Suppl* 2007; **(72)**: 39-41 [PMID: 17982876 DOI: 10.1007/978-3-211-73574-9_6]

P- Reviewers: Carassiti M, Fink MP, Stover CM, Yao YM
S- Editor: Song XX **L- Editor**: A E- Editor: Wu HL

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i2.55

World J Crit Care Med 2014 May 4; 3(2): 55-60
ISSN 2220-3141 (online)

BRIEF ARTICLE

Arterial *vs* venous blood gas differences during hemorrhagic shock

Kristopher Burton Williams, Ashley Britton Christmas, Brant Todd Heniford, Ronald Fong Sing, Joseph Messick

Kristopher Burton Williams, Ashley Britton Christmas, Brant Todd Heniford, Ronald Fong Sing, Joseph Messick, Department of Surgery, Carolinas HealthCare System, Charlotte, NC 28204, United States

Author contributions: Heniford BT, Sing RF, Messick J designed research; Sing RF, Messick J performed research; Messick J contributed new reagents or analytic tools; Christmas AB, Heniford BT, Sing RF analyzed data; Williams KB, Christmas AB, Heniford BT, Sing RF wrote the paper; Messick J deceased since the completion of this study.

Supported by Carolinas HealthCare System, Department of Surgery, Charlotte, North Carolina, United States

Correspondence to: Ronald Fong Sing, DO, FACS, FCCM, Department of Surgery, Carolinas HealthCare System, 1000 Blythe Boulevard, Charlotte, NC 28203, United States. ron.sing@carolinashealthcare.org
Telephone: +1-704-3551311 Fax: +1-704-3555619

Received: March 1, 2013 Revised: October 19, 2013
Accepted: March 3, 2014
Published online: May 4, 2014

Abstract

AIM: To characterize differences of arterial (ABG) and venous (VBG) blood gas analysis in a rabbit model of hemorrhagic shock.

METHODS: Following baseline arterial and venous blood gas analysis, fifty anesthetized, ventilated New Zealand white rabbits were hemorrhaged to and maintained at a mean arterial pressure of 40 mmHg until a state of shock was obtained, as defined by arterial pH $\leqslant$ 7.2 and base deficit $\leqslant$ -15 mmol/L. Simultaneous ABG and VBG were obtained at 3 minute intervals. Comparisons of pH, base deficit, pCO_2, and arteriovenous (a-v) differences were then made between ABG and VBG at baseline and shock states. Statistical analysis was applied where appropriate with a significance of $P < 0.05$.

RESULTS: All 50 animals were hemorrhaged to shock status and euthanized; no unexpected loss occurred. Significant differences were noted between baseline and shock states in blood gases for the following parameters: pH was significantly decreased in both arterial (7.39 ± 0.12 to 7.14 ± 0.18) and venous blood gases (7.35 ± 0.15 to 6.98 ± 0.26, $P < 0.05$), base deficit was significantly increased for arterial (-0.9 ± 3.9 mEq/L *vs* -17.8 ± 2.2 mEq/L) and venous blood gasses (-0.8 ± 3.8 mEq/L *vs* -15.3 ± 4.1 mEq/L, $P < 0.05$). pCO_2 trends (baseline to shock) demonstrated a decrease in arterial blood (40.0 ± 9.1 mmHg *vs* 28.9 ± 7.1 mmHg) but an increase in venous blood (46.0 ± 10.1 mmHg *vs* 62.8 ± 15.3 mmHg), although these trends were non-significant. For calculated arteriovenous differences between baseline and shock states, only the pCO_2 difference was shown to be significant during shock.

CONCLUSION: In this rabbit model, significant differences exist in blood gas measurements for arterial and venous blood after hemorrhagic shock. A widened pCO_2 a-v difference during hemorrhage, reflective of poor tissue oxygenation, may be a better indicator of impending shock.

Key words: Hemorrhagic shock; pH; Base deficit; Arterial blood gases; Venous blood gases

Core tip: Recent studies regarding early goal directed therapy and damage control resuscitation have indicated a potential role for calculated arteriovenous pCO_2 differences in monitoring resuscitative efforts. In a rabbit model of hemorrhagic shock, we demonstrate significant derangements between arterial and venous blood and, while not a novel concept, explore the potential of central venous pCO_2 as an indicator of hemorrhagic shock. Our results demonstrate a widened arteriovenous pCO_2 difference is significantly associated with hemorrhagic shock and may be a more reliable

indicator of inadequate tissue perfusion and therefore impending circulatory collapse.

Williams KB, Christmas AB, Heniford BT, Sing RF, Messick J. Arterial *vs* venous blood gas differences during hemorrhagic shock. *World J Crit Care Med* 2014; 3(2): 55-60 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i2/55.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i2.55

INTRODUCTION

Circulatory collapse is a definitive indicator of the shock state, but may manifest late during hemorrhage leading to delayed diagnosis, resuscitation, and treatment when clinical metrics of circulatory collapse (hypotension, tachycardia, decreased organ perfusion, altered mental status, *etc.*) are the sole measures of a patient's physiologic status. Robust compensatory responses to injury in young, healthy patients can delay treatment of hemorrhage even further as clinical parameters defining shock may not be evident until later stages in the clinical course. Any delay in diagnosis and treatment during massive hemorrhage will likely result in increased morbidity and mortality, fueling the search for adequate trauma resuscitation protocols, such as damage control resuscitation, as well as reliable early markers of impending or ongoing shock[1].

Serologic markers including pH, base deficit, central venous oxygen saturation and lactate have been used to identify and quantitate shock[2-6]. Arterial blood gas analysis is considered the gold standard to determine oxygenation and acid-base status in the acutely injured as well as critically ill and repeat testing offers a means of monitoring resuscitation efforts. However, serious, albeit rare, complications of arterial cannulation (pseudoaneurysm, hematoma, hemorrhage, limb ischemia, infection, neurologic injury)[7] have led to a search for less invasive means of detecting impending shock, quantitating the degree of shock as well as measuring adequate resuscitation. As such, many studies have examined the reliability and accuracy of central venous blood gas in acid-base monitoring as an alternative to arterial blood gas analysis[8-11]. In previous animal models of severely reduced cardiac output, venous hypercarbia has been shown to correlate with inadequacy of tissue perfusion[12,13] and changes in venous blood were noted to occur with greater magnitude and earlier in the process of clinical deterioration than those of arterial blood[14,15]. Similar discrepancies in arterial and venous pCO_2 have been reported in human studies of shock states, as well as the paradox of venous acidemia occurring simultaneously with arterial alkalemia, and have been suggestive of the role of serum pCO_2 differences as an indicator of tissue perfusion[16-20]. In a recent clinical study highlighting the importance of serum pCO_2 in surgical outcomes, Silva *et al*[21] showed a preoperative arteriovenous pCO_2 gap greater than 5.0 mmHg in high risk patients to be predictive of increased in-hospital mortality, circulatory shock, renal failure, intensive care unit (ICU) infection, and length of stay. These previous studies suggest the usefulness of venous blood gas analysis in identifying hemorrhagic shock earlier than other serum markers obtained from arterial blood analysis as well as the potential to accurately monitor adequate resuscitative efforts.

The purpose of this study was to examine the effectiveness of venous blood gas analysis in comparison to the gold standard of arterial blood gas analysis in a rabbit model of hemorrhagic shock.

MATERIALS AND METHODS

Following approval by the Institutional Animal Care and Use Committee of the Carolinas Medical Center, fifty New Zealand white rabbits weighing 3 to 6 kg were anesthetized with 1.0 to 1.5 mL/kg of sodium pentobarbital (25 mg/mL) through an ear vein. Anesthesia was maintained throughout the experiment with 0.5-1.0 mL/kg of intravenous sodium pentobarbital (12.5 mg/mL) as needed, determined by response to a pain stimulus. Adequately anesthetized animals then underwent a tracheotomy and endotracheal ventilation. Tidal volumes of 10 mL/kg were administered by a mechanical ventilator (Siemens 900C Servo ventilator, Berlin, Germany) and fraction of inspired oxygen (FiO_2) was maintained at 0.5.

In all animals, bilateral groin dissection was performed to adequately expose femoral vasculature. Venous access was obtained *via* right femoral vein using a 5.0 French catheter advanced into the level of the right atrium and was utilized for drug infusion as well as withdrawal of venous blood samples. Arterial access was secured *via* left femoral artery utilizing a 3.5 French catheter advanced into the distal abdominal aorta for monitoring of blood pressure, heart rate and arterial blood sampling.

Following baseline arterial and venous blood gas measurements (Radiometer analyzer, ABL-520 #2, Copenhagen, Denmark), animals were hemorrhaged to a mean arterial pressure of 40 mmHg as determined by a multichannel recorder (MT95k2, Astro-Med, Inc., West Warwick, RI). Simultaneous arterial and venous blood gases were obtained every 3 min until hemorrhagic shock was observed, as defined by an arterial pH less than 7.2 and a base deficit greater than or equal to -15 mmol/L. Once the shock state was obtained, animals were then euthanized by intravenous administration of sodium pentobarbital. To minimize procedural variation, all animals were anesthetized, instrumented, hemorrhaged, and euthanized using identical technique by the same investigator.

Statistical analysis

Data was stored and analyzed using SAS software version 9.3 (SAS Inc., Cary, North Carolina). Obtained arterial and venous blood gases were compared to baseline measurements with regard to pH, base deficit and pCO_2. Arteriovenous differences for each parameter (pH, base deficit, pCO_2) were then calculated at baseline and shock. Statistical analysis was performed using the unpaired t-test

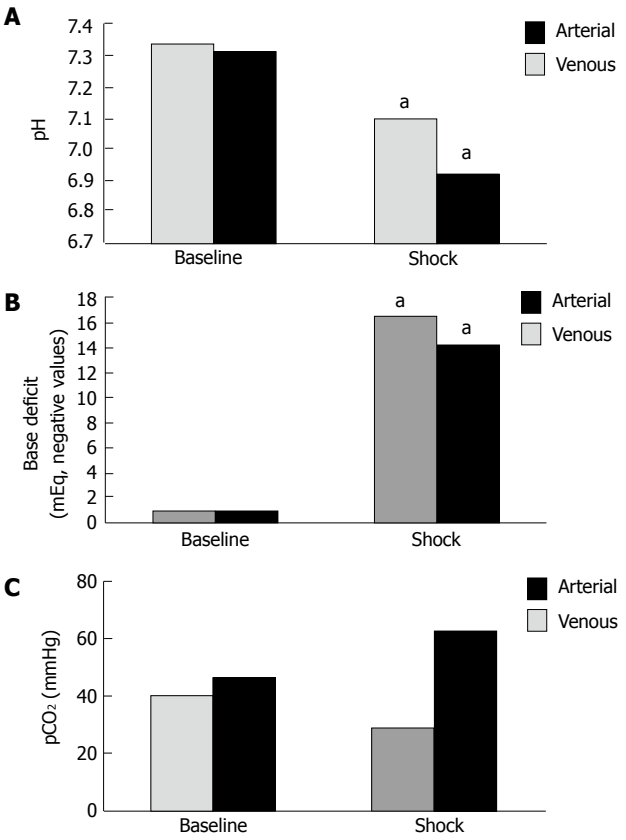


Figure 1 Arterial and venous blood gas at baseline and shock states. [a]*P* < 0.05 *vs* control group. A: pH; B: Base deficit; C: pCO_2.

or Wilcoxon rank sum test where appropriate. For all comparisons, statistical significance was set at a *P* value of less than 0.05.

RESULTSAll 50 animals underwent successful administration of anesthesia, groin dissection, instrumentation, hemorrhage to a state of shock and euthanization without any unexplained or premature losses. Data are expressed as mean ± SD.

Arterial and venous blood gases at baseline and the hemorrhagic shock state

Mean values for pH were significantly decreased from baseline to shock ($P < 0.05$) in both arterial (7.39 ± 0.12 to 7.14 ± 0.18) and venous (7.35 ± 0.15 to 6.98 ± 0.26) blood gases (Figure 1A). Figure 1B compares mean values obtained for base deficit at the 2 physiologic states; a significant increase ($P < 0.05$) was seen in arterial (-0.9 ± 3.9 mEq/L *vs* -17.8 ± 2.2 mEq/L) and venous (-0.8 ± 3.8 mEq/L *vs* -15.3 ± 4.1 mEq/L) base deficit during shock. In comparing pCO_2 at baseline and shock, a non-significant decrease was observed in arterial pCO_2 (40.0 ± 9.1 mmHg *vs* 28.9 ± 7.1 mmHg, $P > 0.05$), while venous blood samples demonstrated a non-significant trend towards increased pCO_2 (46.0 ± 10.1 mmHg *vs* 62.8 ± 15.3 mmHg, $P > 0.05$), as shown in Figure 1C.

Blood gas arteriovenous differences at baseline and the hemorrhagic shock state

Arteriovenous differences in pH, base deficit, and pCO_2 at baseline and the hemorrhagic shock state are represented. No significant differences were seen in calculated differences at baseline for pH (0.04 ± 0.03), base deficit (0.01 ± 3.07 mEq/L), or pCO_2 (5.8 ± 7.5 mmHg), although venous pH demonstrated a larger non-significant trend toward acidosis and a larger non-significant base deficit was seen for arterial samples. In the shock state, a significant difference was noted for arteriovenous pCO_2 difference (34.0 ± 3.10 mmHg, $P < 0.05$), however, calculated differences for pH (0.16 ± 0.08) and base deficit (2.56 ± 3.10 mEq/L) were not significant.

DISCUSSION

Our results demonstrated significant parallel trends of acidosis and increased base deficit in both arterial and venous blood during hemorrhagic shock in a rabbit model (Figure 1A and B). The arteriovenous pCO_2 difference during shock was also statistically significant as venous hypercarbia was observed with simultaneous arterial hypocarbia (Figure 1C).

During hemorrhagic shock, oxygen delivery to tissues is reduced due to lack of red blood cell mass and, subsequently, hemoglobin concentration is insufficient to meet tissue oxygen demands[22]. Contributing to the drop in oxygen carrying capacity, decreased cardiac output secondary to reduced venous return slows the delivery and elimination of venous CO_2 in the lungs and augments ongoing venous hypercarbia[13,18,23]. Reduced oxygen delivery to tissues results in a shift from aerobic toward anaerobic cellular metabolism effecting subsequent production of organic acids, such as lactate, and ensuing acidosis and hypercarbia[17]. When the oxygen supply can be restored quickly, metabolic function can return to normal; however, when the oxygen insufficiency is prolonged, cells become irreversibly damaged and are unable to function in normal energy metabolism[24]. Serum and tissue acidosis develop in direct proportion to the amount and acuity of hemorrhagic shock[2,3,6,14,25].

Studies in both animal models and humans have demonstrated a pronounced dissociation between the arterial and venous pCO_2 during periods of decreased oxygen delivery as a consequence of decreased cardiac output, such as cardiac tamponade[15], severe hemorrhagic shock[2,14], hemodynamic instability[5,17,18,20] or septic shock[16,19]. Carbon dioxide accumulates very rapidly during hemodynamic compromise, as with massive blood loss, before significant amounts of organic acids are detectable in blood since the normal liver is capable of upregulating lactate metabolism early in the hemorrhagic process[15,21]. Mixed venous CO_2 ($CvCO_2$) can be represented according to the Fick equation, $CvCO_2 = VCO_2/Q + CaCO_2$, where VCO_2 represents CO_2 production in tissues, Q signifies cardiac output, and $CaCO_2$ denotes the arterial CO_2 content. Carbon dioxide is released into the circulation at the tissue-venous interface, represented by VCO_2/Q, and is eliminated at the alveolar-arteriole interface in the lungs, represented by $CaCO_2$. Under conditions of normal cardiac output and venous return,

there is adequate ventilatory elimination of CO_2 that is produced in the tissues and acid-base equilibrium is established. However, as cardiac output and venous return decrease, the increased CO_2 produced from anaerobic tissues cannot be effectively eliminated by the lungs, resulting in a disconnect between arterial and venous vascular trees whereby arterial blood gases reflect CO_2 exchange at the alveolar-arterial level while venous blood gases are indicative of acid-base status and oxygenation at the level of the tissues. Examining the Fick equation, it can be seen that as cardiac output (Q) declines with simultaneous increased tissue CO_2 production (VCO_2), mixed venous CO_2 ($CvCO_2$) will increase. This was demonstrated in our rabbit hemorrhage model in which the animals were adequately ventilated but hypoperfused, resulting in hypercarbia detected in venous but not arterial blood gas analysis, representing insufficient oxygen delivery to tissues. Therefore, venous blood gas values may better reflect insufficient oxygen delivery to the tissues and subsequent impending shock. Although our results did not show a statistically significant difference in the arteriovenous pH gradient, the venous samples were markedly more acidic than the arterial samples taken during the shock state (Figure 1A).

The clinical utility of arteriovenous pCO_2 differences in goal directed therapy (GDT) has recently been addressed in the literature. In a series of septic ICU patients resuscitated to a mixed venous oxygen saturation goal of 70% or greater, Vallée *et al*[16] demonstrated those patients with arteriovenous pCO_2 differences greater than 6 mmHg had higher lactate concentrations and lower lactate clearance rates than those with arteriovenous pCO_2 differences less than 6 mmHg, subsequently reflecting the status of global tissue perfusion. They further demonstrated lower cardiac indexes in those patients with arteriovenous pCO_2 values greater than 6 mmHg following "adequate" resuscitation to a mixed venous oxygen saturation of 70% as compared to the cohort of patients with arteriovenous pCO_2 values less than 6 mmHg. Similarly, Futier *et al*[26] demonstrated larger arteriovenous pCO_2 differences to be significantly associated with post-operative complications in "adequately resuscitated" patients (to a mixed venous oxygen saturation goal greater than 71%) undergoing major abdominal surgery. These clinical results indicate further optimization of GDT may be obtained through a combination of mixed venous oxygenation and arteriovenous pCO_2 difference analysis, potentially playing vital roles in progressive damage control resuscitation models in trauma[1].

Some shortcomings of the current study deserve discussion. First, this study was not conducted in a spontaneously-breathing animal model, effectively eliminating the possibility of respiratory compensation which likely will occur in cases of acute injury and hemorrhage. To address this criticism, Mathias *et al*[15] performed acid-base comparisons between arterial and venous blood gases in a spontaneously-breathing, under-anesthetized canine model of acute cardiac tamponade and found a similar paradox of venous acidosis and hypercarbia with concomitant arterial alkalemia and hypocarbia, even in the early stages of decreased cardiac output (20%) prior to any reduction in arterial blood pressure. Although the criticisms of performing these studies in animal models with blunted or absent respiratory compensatory mechanisms are valid concerns, the results of Mathias *et al*[15] indicate the paradoxical acid-base trends are still evident in a minimally-anesthetized, spontaneously-breathing, non-ventilated animal model. Also, performing these studies in live animal models without sufficient sedation or supportive measures, such as ventilatory support, would certainly be considered distressful to the animals. A second shortcoming of this study is the lack of a temporal metric for the onset of acid-base changes in our animal model, as well as a lack of serum lactate analysis. It would be beneficial to define the chronological relationship of arterial hypocapnea, venous hypercapnea and acidosis in comparison to the accumulation of lactate during the course of hemorrhagic shock in the rabbit model to better define the usefulness of venous blood gas in the course of hemorrhagic shock.

Our study in a rabbit model indicates hemorrhage shock results in significant acidosis and base deficit in both arterial and venous blood with a significant arteriovenous pCO_2 difference of venous hypercarbia and arterial hypocarbia, consistent with previously reported disparities between arterial and venous pCO_2 in the setting of severely hypoperfused states. These results indicate that venous blood gas analysis may be a superior indicator of cellular hypoperfusion in hemorrhagic shock, as evidenced by pronounced hypercarbia, and may be more reflective of tissue oxygenation compared to arterial blood gas analysis. Further studies are needed to determine if venous blood gas analysis is a more rapid indicator of impending circulatory collapse or is a more accurate gauge of adequate resuscitative efforts.

COMMENTS

Background

Early and adequate tissue perfusion is a key tenet of goal-directed therapy and damage control resuscitation, employed in critical care and trauma practices, respectively. Arteriovenous differences in pCO_2 have demonstrated potential in the early detection of insufficient tissue perfusion as well as the quantification of resuscitative efforts.

Research frontiers

Establishment of an early, reliable, and easily obtainable marker for impending circulatory collapse in hemorrhagic shock would contribute significantly to treatment algorithms, possibly allowing supportive measures (fluid resuscitation, blood product administration, vasopressor circulatory support, *etc.*) to be initiated prior to classic physiologic indicators of circulatory collapse. However, no such definitive marker has been elucidated. In this study, the authors demonstrate significant similarities and differences in arterial and venous blood gas derangements, focusing on the arteriovenous differences noted in a rabbit model of hemorrhagic shock in an effort to further define arteriovenous pCO_2 differences as a potential early indicator of inadequate tissue perfusion.

Innovations and breakthroughs

Previous studies have examined arterial and venous blood gas derangements (pH, base deficit, lactate levels, oxygen saturation) in states of hypoperfusion in animal models as well as humans. Paradoxical venous hypercarbia with arterial hypocarbia associated with decreased cardiac output has also been reported in

the literature, suggesting a role for pCO_2 monitoring in cases of hypoperfused states. In this study, authors conclusively demonstrated a widened pCO_2 difference (venous hypercarbia with concomitant arterial hypocarbia) is associated with hemorrhagic shock in a novel rabbit model.

Applications

The results of this study, viewed in light of recent work regarding venous blood gas analysis in hypoperfused states, further supports the prospect that central venous blood gas pCO_2 differences may indicate effectiveness of resuscitative efforts in the acutely injured hemorrhagic state. Certainly, further human studies in the setting of acute hemorrhage deserve attention so that a more rapid, accurate and easily obtainable mechanism of resuscitation may be elucidated.

Terminology

The term arteriovenous pCO_2 difference is used to describe the absolute value of the quantifiable variance between arterial blood gas pCO_2 and venous blood gas pCO_2. This is represented in units of mmHg, a standard unit of measurement for partial pressure.

Peer review

This is a well-written manuscript which analyzes the effects of hemorrhagic shock on arterial and venous blood gases in a rabbit animal model. An added caveat is the significant widened arteriovenous pCO_2 difference seen in the shock state. The manuscript also reviews pertinent publications on the subject, highlighting recent clinical studies which suggest a role for arteriovenous pCO_2 differences in monitoring resuscitation. Although not novel, the results certainly provide further evidence that widened pCO_2 differences are indicative of worsening shock and may therefore possibly be another tool in our armament to monitor resuscitation.

REFERENCES

1 **Cotton BA**, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, Gill BS, Albarado R, McNutt MK, Holcomb JB. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg* 2011; **254**: 598-605 [PMID: 21918426 DOI: 10.1097/SLA.0b013e318230089e]

2 **Rixen D**, Siegel JH. Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. *Crit Care* 2005; **9**: 441-453 [PMID: 16277731]

3 **Rossaint R**, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR. Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010; **14**: R52 [PMID: 20370902 DOI: 10.1186/cc8943]

4 **van Beest P**, Wietasch G, Scheeren T, Spronk P, Kuiper M. Clinical review: use of venous oxygen saturations as a goal - a yet unfinished puzzle. *Crit Care* 2011; **15**: 232 [PMID: 22047813 DOI: 10.1186/cc10351]

5 **Hobbs TR**, O'Malley JP, Khouangsathiene S, Dubay CJ. Comparison of lactate, base excess, bicarbonate, and pH as predictors of mortality after severe trauma in rhesus macaques (Macaca mulatta). *Comp Med* 2010; **60**: 233-239 [PMID: 20579439]

6 **Kaplan LJ**, Frangos S. Clinical review: Acid-base abnormalities in the intensive care unit -- part II. *Crit Care* 2005; **9**: 198-203 [PMID: 15774078 DOI: 10.1186/cc2912]

7 **Scheer B**, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care* 2002; **6**: 199-204 [PMID: 12133178]

8 **Malatesha G**, Singh NK, Bharija A, Rehani B, Goel A. Comparison of arterial and venous pH, bicarbonate, PCO2 and PO2 in initial emergency department assessment. *Emerg Med J* 2007; **24**: 569-571 [PMID: 17652681 DOI: 10.1136/emj.2007.046979]

9 **Rudkin SE**, Kahn CA, Oman JA, Dolich MO, Lotfipour S, Lush S, Gain M, Firme C, Anderson CL, Langdorf MI. Prospective correlation of arterial vs venous blood gas measurements in trauma patients. *Am J Emerg Med* 2012; **30**: 1371-1377 [PMID: 22169587 DOI: 10.1016/j.ajem.2011.09.027]

10 **Middleton P**, Kelly AM, Brown J, Robertson M. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J* 2006; **23**: 622-624 [PMID: 16858095 DOI: 10.1136/emj.2006.035915]

11 **Malinoski DJ**, Todd SR, Slone S, Mullins RJ, Schreiber MA. Correlation of central venous and arterial blood gas measurements in mechanically ventilated trauma patients. *Arch Surg* 2005; **140**: 1122-1125 [PMID: 16342377]

12 **Dubin A**, Edul VS, Pozo MO, Murias G, Canullán CM, Martins EF, Ferrara G, Canales HS, Laporte M, Estenssoro E, Ince C. Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. *Crit Care Med* 2008; **36**: 535-542 [PMID: 18216603 DOI: 10.1097/01.CCM.0000300083.74726.43]

13 **Vallet B**, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol* (1985) 2000; **89**: 1317-1321 [PMID: 11007564]

14 **Oropello JM**, Manasia A, Hannon E, Leibowitz A, Benjamin E. Continuous fiberoptic arterial and venous blood gas monitoring in hemorrhagic shock. *Chest* 1996; **109**: 1049-1055 [PMID: 8635330]

15 **Mathias DW**, Clifford PS, Klopfenstein HS. Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs. *J Clin Invest* 1988; **82**: 833-838 [PMID: 3417872 DOI: 10.1172/JCI113686]

16 **Vallée F**, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii K, Fourcade O, Genestal M. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med* 2008; **34**: 2218-2225 [PMID: 18607565 DOI: 10.1007/s00134-008-1199-0]

17 **Mekontso-Dessap A**, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, Teboul JL. Combination of veno-arterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. *Intensive Care Med* 2002; **28**: 272-277 [PMID: 11904655 DOI: 10.1007/s00134-002-1215-8]

18 **Teboul JL**, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. *Crit Care Med* 1998; **26**: 1007-1010 [PMID: 9635647]

19 **Mecher CE**, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. *Crit Care Med* 1990; **18**: 585-589 [PMID: 2111753]

20 **Cuschieri J**, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med* 2005; **31**: 818-822 [PMID: 15803301 DOI: 10.1007/s00134-005-2602-8]

21 **Silva JM**, Oliveira AM, Segura JL, Ribeiro MH, Sposito CN, Toledo DO, Rezende E, Malbouisson LM. A large Venous-Arterial PCO(2) Is Associated with Poor Outcomes in Surgical Patients. *Anesthesiol Res Pract* 2011; **2011**: 759792 [PMID: 22007204 DOI: 10.1155/2011/759792]

22 **Hsia CC**. Respiratory function of hemoglobin. *N Engl J Med* 1998; **338**: 239-247 [PMID: 9435331 DOI: 10.1056/NEJM199801223380407]

23 **Funk DJ**, Jacobsohn E, Kumar A. Role of the venous return in critical illness and shock: part II-shock and mechanical ventilation. *Crit Care Med* 2013; **41**: 573-579 [PMID: 23263572 DOI: 10.1097/CCM.0b013e31827bfc25]

24 **Bruegger D**, Kemming GI, Jacob M, Meisner FG, Wojtczyk CJ, Packert KB, Keipert PE, Faithfull NS, Habler OP, Becker BF, Rehm M. Causes of metabolic acidosis in canine hemorrhagic shock: role of unmeasured ions. *Crit Care* 2007; **11**: R130 [PMID: 18081930 DOI: 10.1186/cc6200]

25 **Theusinger OM**, Thyes C, Frascarolo P, Schramm S, Seifert B, Spahn DR. Mismatch of arterial and central venous

blood gas analysis during haemorrhage. *Eur J Anaesthesiol* 2010; **27**: 890-896 [PMID: 20601892 DOI: 10.1097/EJA.0b013e32833adea8]

26 **Futier E**, Robin E, Jabaudon M, Guerin R, Petit A, Bazin JE, Constantin JM, Vallet B. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care* 2010; **14**: R193 [PMID: 21034476 DOI: 10.1186/cc9310]

P- Reviewers: Chen XL, Mohta M, Nayci A **S- Editor**: Gou SX
L- Editor: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i2.61

World J Crit Care Med 2014 May 4; 3(2): 61-67
ISSN 2220-3141 (online)

BRIEF ARTICLE

Variable change in renal function by hypertonic saline

Jesse J Corry, Panayiotis Varelas, Tamer Abdelhak, Stacey Morris, Marlisa Hawley, Allison Hawkins, Michelle Jankowski

Jesse J Corry, Panayiotis Varelas, Tamer Abdelhak, Stacey Morris, Marlisa Hawley, Allison Hawkins, Department of Neurology, Henry Ford Hospital, Marshfield, WI 54449, United States
Jesse J Corry, Panayiotis Varelas, Tamer Abdelhak, Department of Neurosurgery, Henry Ford Hospital, Marshfield, WI 54449, United States
Michelle Jankowski, Department of Biostatistics, Henry Ford Hospital, Marshfield, WI 54449, United States
Author contributions: Corry JJ contributed to study concept and design, data review, statistical analysis and review, manuscript authorship; Varelas P and Abdelhak T participated in data review, manuscript authorship and editing; Morris S, Hawley M and Hawkins A contributed to data collection, manuscript editing; Jankowski M contributed to statistical analysis, manuscript methods authorship and editing; all authors approved final revision.
Correspondence to: Jesse J Corry, MD, Department of Neurology, Henry Ford Hospital, Marshfield, 000 N. Oak Avenue, 4F3, Marshfield, WI 54449,
United States. corry.jesse@marshfieldclinic.org
Telephone: +1-715-079562 Fax: +1-715-3875727
Received: September 16, 2013 Revised: December 9, 2013
Accepted: January 13, 2014
Published online: May 4, 2014

Abstract

AIM: To investigate the effects of hypertonic saline in the neurocritical care population.

METHODS: We retrospectively reviewed our hospital's use of hypertonic saline (HS) since March of 2005, and prospectively since October 2010. Comparisons were made between admission diagnoses, creatinine change (Cr), and HS formulation (3% NaCl, 3% NaCl/sodium acetate mix, and 23.4% NaCl) to patients receiving normal saline or lactated ringers. The patients (n = 1329) of the retrospective portion were identified. The data presented represents the first 230 patients with data.

RESULTS: Significant differences in Acute Physiology and Chronic Health Evaluation Ⅱ scores and Glasgow Coma Scale scores occurred between different saline formulations. No significant correlation of Cl^- or Na^+ with Cr, nor with saline types, occurred. When dichotomized by diagnosis, significant correlations appear. Traumatic brain injury (TBI) patients demonstrated moderate correlation between Na^+ and Cr of 0.45. Stroke patients demonstrated weak correlations between Na^+ and Cr, and Cl^- and Cr (0.19 for both). Patients receiving HS and not diagnosed with intracerebral hemorrhage, stroke, subarachnoid hemorrhage, or TBI demonstrated a weak but significant correlation between Cl^- and Cr at 0.29.

CONCLUSION: Cr directly correlates with Na^+ or Cl^- in stroke, Na^+ in TBI, and Cl^- in other populations. Prospective comparison of HS and renal function is needed.

Key words: Hypertonic saline solution; Sodium chloride; Acute kidney injury; Cerebral edema; Critical care

Core tip: This work adds to the literature that changes in Na^+ and Cl^- in the neurocritical care population correlate to adverse changes in renal function. It is critical for the neurointensivist to remain cognizant of this when choosing whether or not to use hypertonic saline, and what to monitor when doing so. Unlike previous work, this data suggests some diseases may have more or less a change in renal function from Na^+ or Cl^-. This argues for further study of how the formulations of these fluids may change outcome in the neurocritically ill.

Corry JJ, Varelas P, Abdelhak T, Morris S, Hawley M, Hawkins A, Jankowski M. Variable change in renal function by hypertonic saline. *World J Crit Care Med* 2014; 3(2): 61-67 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i2/61.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i2.61

INTRODUCTION

A nearly ubiquitous problem in the neurocritical care population is cerebral edema (CE). Cerebral edema has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of intracerebral pressure (ICP)[1]. The role of CE in outcome is contentious, with evidence suggesting that the extent of CE may, and may not, correlate with outcome[2-6]. Animal models of CE demonstrate increased water content of edematous tissue correlates with inflammation and neuronal death[7]. Potentially, reduction of this edema may reduce the degree of neuronal death, potentially improving outcome and decreasing hospital length-of-stay.

The medical management of CE is not without problems. Mannitol use is common, but is complicated by deleterious effects on renal function, fluctuations in intravascular volume, and pH. Over time, mannitol' s slow elimination from the cerebrospinal fluid may require progressively higher doses to control ICP and rebound CE[8,9]. Increasingly, hypertonic saline (HS) is being used to abate cerebral edema. Used in bolus or a continuous infusion fashion, HS has been shown to be safe and effective in reducing ICP in patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and stroke[10,11]. HS shifts fluid from endothelium and surrounding tissues into the vascular compartment, normalizing the endothelia volume, increasing capillary diameter, and reducing resistance to flow[12]. Edema can be reduced in this manner. Further, hypertonic fluids produce smooth muscle vasodilation improving regional blood flow[12]. HS is relatively inexpensive. The early use of HS may reduce secondary cell injury caused by cerebral edema[13]. These characteristics make HS an ideal therapeutic option in conditions such as SAH, intracerebral hemorrhage (ICH), stroke, and TBI.

However, the use of HS has not demonstrated any survival or outcome benefit despite reductions in ICP[12,14]. Further, HS may be associated with increased risk-of blood-stream infections, and possibly increased risk-of nosocomial and urinary tract infections[14]. A growing body of evidence suggests a possible link between HS use, renal dysfunction, and mortality[15-17]. We hypothesize the use of HS correlates to adverse changes in renal function.

MATERIALS AND METHODS

Study setting

The Henry Ford Neurocritical Care Unit (NCCU) is a 16 bed unit with a yearly census over 1000 patients. The Henry Ford Neurocritical Database records data on stroke, TBI, ICH, SAH, SE, and spinal cord injury patient populations admitted to the NCCU. The data has been prospectively collected since October of 2010, with data added retrospectively from March of 2005 (when the first neurointensivist joined the staff) until October 2010. Between March 2005 and October 2010, 1329 patients of the retrospective cohort meet the inclusion criteria. The data presented represents the first 230 patients with data.

Study design

With institutional review board approval, we mined the Henry Ford Neurocritical Database to identify all patients from March of 2005 to October 2010 with the aforementioned diagnosis who received HS. These patients were cross matched with the institution's pharmacy database to ascertain which saline formulation patients in the retrospective cohort received. In this retrospective sample, if patients were identified who received HS, and were not in the NCCU database, their data was retrospectively collected. Data was collected from admission until NCCU discharge, death, or post admission day (PAD) 13. Variables sought included: (1) IVF formulation: Normal saline (NS), ringer's lactate (LR), HS (3% NaCl, 3% NaCl:Na acetate, 23.4%); (2) physiologic: Mean arterial pressure; serum sodium, creatinine, chloride, HCO_3, BUN, creatinine; admission weight; (3) clinical: Admission Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) scores, admission Glasgow coma scale in all patients, Hunt and Hess grade in SAH patients, NIH stroke scale in stroke patients, presence of external ventricular drain, and duration of ICU stay. APACHE Ⅱ scores were retrospectively calculated on all patients in the retrospective cohort; and (4) demographics: Age; sex; race; presence of hypertension, diabetes, pre-existing of renal insufficiency and etiology of renal insufficiency, history of coronary artery disease or congestive heart failure. Patients received various formulations of HS at the discretion of the attending NCCU staff. Correlations to renal function, as measured by Cr, to the formulation of saline used, and to changes in serum sodium and chloride levels were made. Patients receiving only LR o rNS served as a comparison group.

Statistical analysis

Intervariable associations were calculated between using Pearson's correlation coefficients. The *P* values for these correlation coefficients were computed using clustering methods that take into account the multiple measures from the same patient. This was done with the entire sample as well as within each saline type and within each diagnosis type.

RESULTS

Who received HS solutions?

Table 1 summarizes the baseline characteristics of this cohort. There were no significant differences in diagnosis between groups. There were significant differences in the APACHE Ⅱ scores and Glasgow Coma Scale (GCS) scores between the different formulations of HS. Significant differences emerged in admission Na^+, A-a gradient, APACHE Ⅱ score, and GCS. In pairwise comparisons, patients receiving HS demonstrated higher APACHE Ⅱ scores and lower GCSv scores. 3% patients uniformly scored lower on GCS components compared to LR/NS patients, and lower in the GCSm and GCSe

Table 1 Baseline characteristics by saline type

Variable	23.40% (*n* = 22)	3% (*n* = 13)	NS/LR (*n* = 194)	*P* value
Diagnosis				0.078
ICH	15 (68)	7 (54)	67 (35)	
Other	3 (14)	3 (23)	47 (24)	
SAH	4 (18)	2 (15)	43 (22)	
Stroke	0 (0)	0 (0)	28 (14)	
TBI	0 (0)	1 (8)	9 (5)	
Age (yr)	61.9 ± 15.6	59.2 ± 19.6	56.8 ± 16.2	0.356
HCT (mmHg)	38.2 ± 6.9	38.1 ± 6.2	38.1 ± 7.0	0.999
WBC (10^9/L)	12.5 ± 6.2	11.6 ± 5.2	11.4 ± 9.1	0.865
Temperature (℃)	37.3 ± 0.9	37.2 ± 0.7	36.8 ± 2.5	0.514
HR	81.3 ± 20.3	86.5 ± 19.1	82.6 ± 16.7	0.668
RR	18.1 ± 4.6	17.5 ± 7.3	18.6 ± 4.4	0.633
MAP	98.3 ± 18.2	100.8 ± 33.2	106.5 ± 24.8	0.267
Na	141.5 ± 6.4	8.2 ± 5.3	139.0 ± 4.1	0.037
K	3.9 ± 0.6	3.7 ± 0.5	4.0 ± 2.0	0.888
Glasgow coma Scale (verbal)	2.6 ± 1.7	2.3 ± 1.5	3.4 ± 1.7	0.010
1	10 (45)	6 (46)	53 (27)	
2	1 (5)	2 (15)	10 (5)	
3	2 (9)	1 (8)	15 (8)	
4	5 (23)	3 (23)	29 (15)	
5	4 (18)	1 (8)	87 (45)	
Glasgow Coma Scale (motor)	5.0 ± 1.5	3.9 ± 1.8	5.3 ± 1.3	0.002
1	1 (5)	1 (8)	5 (3)	
2	1 (5)	3 (23)	4 (2)	
3	2 (9)	2 (15)	16 (8)	
4	2 (9)	1 (8)	13 (7)	
5	4 (18)	2 (15)	27 (14)	
6	12 (55)	4 (31)	129 (66)	
Glasgow coma Scale (eyes)	2.9 ± 1.3	2.0 ± 1.0	3.3 ± 1.1	< 0.001
1	5 (23)	5 (38)	28 (14)	
2	4 (18)	4 (31)	15 (8)	
3	2 (9)	3 (23)	31 (16)	
4	11 (50)	1 (8)	120 (62)	
A aGrad[1]	6.1 ± 195.3	173.7 ± 141.2	125.3 ± 154.9	0.024
pH[2]	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	0.306
PCO_2[3]	27.0 ± 1.7	27.0 ± 3.0	26.0 ± 3.3	0.756
PaO_2	209.2 ± 114.6	189.5 ± 136.8	150.8 ± 115.1	0.053
Baseline Cr	1.3 ± 1.4	0.9 ± 0.3	1.4 ± 1.8	0.655
APACHE Ⅱ	14.9 ± 7.6	17.5 ± 5.2	10.7 ± 6.5	< 0.001

[1]23.4%, *n* = 19; 3%, *n* = 12; normal saline/ringer's lactate (NS/LR), *n* = 177; [2]23.4%, *n* = 19; 3%, *n* = 10; NS/LR, *n* = 111; [3]23.4%, *n* = 3; 3%, *n* = 3; NS/LR, *n* = 83. ICH: Intracerebral hemorrhage; TBI: Traumatic brain injury; SAH: Subarachnoid hemorrhage; HCT: Hematocrit; MAP: Mean arterial pressure; APACHE Ⅱ: Admission acute physiology and chronic health evaluation Ⅱ scores.

compared to 23.4% patients (Table 2). This would suggest patients receiving HS, particularly 3% solutions, had a greater illness burden at admission.

What are the effects of HS on renal function?

Table 3 summarizes the effects of HS on renal function in this cohort. No significant correlation occurred with Na^+ or Cl^- with Cr when grouped according to saline type. The correlation between Na^+ and Cr within each of the saline types does not differ much from the overall correlation, except for within the 3% saline group. The correlation for the 3% saline group is 0.256 but this was not statistically significantly different from zero ($P = 0.26$).

Table 2 Pairwise comparisons for those that were significant

Dependent	23.4% *vs* 3%	23.4% *vs* NS/LR	3% *vs* NS/LR
Na^+	0.035	0.016	0.503
A aGrad	0.370	0.009	0.306
Apache Ⅱ	0.261	0.005	< 0.001
GCS v	0.579	0.034	0.019
GCS m	0.027	0.294	< 0.001
GCS E	0.028	0.123	< 0.001

NS/LR: Normal saline/ringer's lactate; APACHE Ⅱ: Admission acute physiology and chronic health evaluation Ⅱ scores; GCS: Glasgow coma scale.

Table 3 Correlations between Cl^-, Na^+ and Cr

Population	Na^+ and Cr			Cl^- and Cr		
	n	Corr	*P* value	*n*	Corr	*P* value
Overall	230	0.025	0.63	229	0.074	0.16
Saline type						
23.40%	22	0.037	0.58	22	0.042	0.65
3%	13	0.256	0.26	13	0.181	0.43
NS/LR	194	0.026	0.65	194	0.097	0.09
Diagnosis type						
ICH	89	0.145	0.10	89	0.058	0.55
Other	53	0.096	0.09	53	0.287	< 0.001
SAH	50	0.125	0.08	50	0.085	0.28
Stroke	28	0.187	< 0.001	28	0.185	0.001
TBI	10	0.447	0.048	10	0.361	0.1

NS/LR: Normal saline/ringer's lactate; ICH: Intracerebral hemorrhage; TBI: Traumatic brain injury; SAH: Subarachnoid hemorrhage.

The same holds true for the correlation between Cl^- and Cr, it is greater in the 3% saline group but still not statistically significantly different from zero ($r = 0.18$, $P = 0.43$). When the correlations were dichotomized by the diagnosis, significant findings appear.

The strongest correlations were found in TBI, patients given HS and not diagnosed with TBI, stroke, SAH, or ICH (other), and stroke. With respect to TBI, a moderate correlation was found between rise in Cr and Na^+. For stroke, weak correlations between rise in Cr and both increases in Na^+ and Cl^- occurred. Patients in this "other" category demonstrated a significant, yet weak, correlation between increases in Cl^- and Cr.

DISCUSSION

Even small increases in creatinine the first two days following admission are predictive of mortality[16,18]. Thus, therapies precipitating kidney injury are concerning. Presentation or development of diminished renal function is a predictor of poor outcome and mortality in stroke, ICH and SAH[19-25]. In the case of ICH, this has been associated with hemorrhage volume and GCS[21,22,26]. Similarly, development of renal dysfunction during hospitalization has been linked to increased mortality and is associated with lower GCS and higher APACHE Ⅲ score in TBI[27,28].

Frequently neurointensivists are asked to control cerebral edema *via* the use of mannitol and HS. Superi-

ority of one agent remains a matter of debate. Not yet recruiting at the time of this manuscript, investigators at Massachusetts General Hospital are investigating if induced, sustained hypernatremia to a goal of 150-160 mmol/L following traumatic brain injury will decrease the rate of cerebral edema formation and improve patient outcomes[29]. One study, sponsored by Indiana University, currently enrolling is looking at 20% mannitol *vs* 3% saline for the treatment of intracranial hypertension[30].

Mannitol appears to reduce ICP through reducing brain water content[31]. However, its use may result in kidney injury and rebound edema[8,9]. Increasingly HS saline is being used in various formulations either as a preventative or acute therapy[12,32]. HS appears to have a number of beneficial effects. In TBI, the use of 23.4% NaCl results in ICP reductions and elevations in cerebral perfusion pressure with commensurate elevations in brain tissue oxygenation[33,34]. These reductions in ICP are most notable in patients with the greatest elevations in ICP. Further, in cerebral hemorrhages ≥ 30 mL, the early use of HS to target a serum sodium between 145-155 mmol/L demonstrates both absolute and relative reductions of cerebral edema when compared to normonatremic patients[32].

These effects appear to be the result of a combination of actions including reduction in brain water content *via* osmotic forces, reductions in peripheral vascular resistance, and arteriolar vasodilatation with improvement in capillary blood flow[12,13,35]. Further, animal models treated with HS have demonstrated reduced aquaporin 4 expression on astrocytes with attenuation of brain water content[13]. In addition, increasing evidence demonstrates HS possesses immune-modulating properties *via* reduction in cytokine production and neutrophil activation[36,37]. Finally, animal models have demonstrated reductions in neuronal apoptosis.

Despite the ample experimental evidence, the clinical use of HS has not demonstrated any survival or outcome benefit and is not without risk[12,14]. Hypernatremia is associated with insulin resistance, reduced hepatic gluconeogenesis and lactate clearance, delirium, rhabdomyolysis, and reduced cardiac function[38,39]. Not surprisingly, ICU acquired elevations or reductions in serum sodium, dysnatremia, are common in neurosurgical and trauma patients, and associated with kidney injury[40]. Further, when compared to normonatremic patients, dysnatremia is associated with increased disease severity, longer length-of-stay, and mortality[40-42].

Our group inquired whether the formulation of saline used affected renal function in the neurocritical care population. The question of IVF formulation affecting patient outcome has been debated for some time. Evidence is increasingly suggesting formulation of saline and/or rapid change in serum sodium or chloride may adversely affect renal function[15-17]. A study in healthy subjects has demonstrated greater natriuresis and sooner time to first post-bolus micturition in those receiving LR *vs* NS[43]. Huang *et al*[16] reported the use of HS in burn patients produced significant increases renal, pulmonary, and cardiac failure compared to LR use. Patients receiving HS had less urine output. Further, the development of renal failure was heralded by a greater initial rise and slower subsequent fall in serum sodium levels during the first week of admission. Although this study was in burn patients, its findings are provocative. More recently, a study evaluating the effects of a Cl^- restrictive *vs* Cl^- liberal usage in critical ill patients demonstrated more acute kidney injury and greater use of renal-replacement therapy in the Cl^- liberal group[44]. Though the populations of these studies differ from the neurocritical care population, this suggests the formulation of saline may have an effect on renal function.

With respect to our initial question, does saline type affect renal function; we found no such correlation in our sample. We found patients receiving HS have higher disease severity as assessed by lower GCS and higher APACHE Ⅱ scores. Not surprisingly, we found sicker patients more frequently received HS in this sample. This correlation has been previously reported[15]. This makes intuitive sense, with evidence suggesting early use of HS may limit the development of CE[32]. Similar to the findings of Aiyagari *et al*[15], Froelich *et al*[17] reported adverse changes in renal function with serum Na^+ > 155 mmol/L. This was not associated with the use or formulation of HS, a finding noted in our study too.

Unexpectedly, when we dichotomized by diagnosis, we found weak to moderate correlations between admitting disease and changes in Cr associated with hyperchloremia or hypernatremia. This was most noted in TBI, stroke, and non-vascular NCCU diagnosis; trends were also noted in ICH and SAH too. The explanation for this association is uncertain. Previous studies demonstrate correlations to Na^+ increase and renal dysfunction[15,17]. Although patients receiving a continuous HS infusion, when compared to a cohort receiving NS, do not have a higher risk of renal dysfunction, a significant correlation between sever hypernatremia and renal dysfunction does exist[17]. This could however reflect a more severe underlying brain injury rather than effect of HS.

Both clinical and experimental literature provides insight as to how Na^+ and Cl^- could adversely affect renal function. HS solutions initially cause renal vasodilatation and increased renal blood flow[45]. It is theorized hypernatremia may produce renal injury *via* intravascular dehydration and vasoconstriction[46]. Canine models undergoing rapid renal artery sodium elevations demonstrate reduced renal blood flow and glomerular filtration rate with inhibition of rennin secretion[47]. Clinical studies have demonstrated hypernatremia is associated with elevations in creatinine in approximately 10% of patients[15]. This noted increase parallels elevations in sodium and APACHE Ⅱ scores, and is inversely related to admission GCS scores. However, save for sodium values > 160 mEq/L hypernatremia is not independently associated with mortality[15,17].

While direct proof linking saline-induced hyperchloremia to nephrotoxicity is not available, a strong cir-

cumstantial case can be made[48]. NS, with 154 mmol/L of chlorine can result in hyperchloremia and an acidosis[43,49]. Elevation in chloride can reduce renal blood flow and decreases the excretion of sodium[43,45]. Hyperchloremia appears to cause a renal vasoconstriction specific to renal vasculature and independent of the renal nerve[45]. This reduction in renal blood flow could precipitate renal ischemia and reducing glomerular filtration rate[45,50]. At the macula densa, Cl^- activates tubuloglomerular feedback by precipitating afferent arteriolar vasoconstriction and decreased glomerular filtration rate[51]. Further, animal models suggest Cl^- increases thromboxane synthesis resulting in renal vasoconstriction and reduced renal blood flow[52].

This single center, retrospective study has a number of limitations. First is the choice of serum creatinine as a biomarker of renal function. Though regularly used to infer kidney health and glomerular filtration, it is at best a crude measure of these. Often creatinine may be insensitive to early, deleterious changes in renal function. Next, given the time and cost of collecting retrospective data, this data represents an interim analysis to see if continued collection of these variables was warranted. As such, its small size and single center nature limit its applicability. Other centers with different demographics or practices may have different outcomes from what is represented here. The retrospective design and single center location limits what questions can be asked, data obtained, and the number of patients available. Regarding the disease specific correlations, a number of deficiencies exist. Regarding TBI, this study did not collect data on vasopressor use, blood pressure targets, or volume received, all variables noted to augment renal blood flow[53]. Intense sympathetic stimulation alters prostaglandin-mediated vasodilatation, resulting in reduced glomerular filtration[54]. Data on antecedent medication use was not collected. Could prior use of medications such as angiotensin converting enzyme inhibitors, in the setting of rapid changes in serum Na^+ and Cl^-, result in diminished renal blood flow? Finally, after dichotomizing by diagnosis, differences in baseline physiologic variables was not assessed. Perhaps these correlations occurred in patients who were inherently more ill when viewed from the perspective of admitting diagnosis. Despite these limitations, this data is provocative in suggesting the admitting disease may affect the physiologic response to a therapy.

This study adds to the literature demonstrating the use of HS is not inherently injurious to renal physiology. Further, we too note the correlation of injury severity to HS use. Finally, our data suggests when viewed from the perspective of admitting diagnosis, HS use may correlate to the development of kidney injury. However, the nature of this correlation needs further exploration. Variables to investigate include rate change of Na^+ and Cl^-; HS administration times over the course of disease; role of premorbid medications; and regional differences in population makeup. Wide variability exists in the treatment of cerebral edema among intensivists[55]. With no clear "right answer" to the question of cerebral edema, more investigation is needed regarding the risks/benefits of the treatments available and the patients who would be best suited for particular therapies. Prospective comparisons of HS formulation and renal function are needed to further assess if formulation affects outcome and cost. Prospective studies are warranted to better define this association and its effect on outcome.

COMMENTS

Background

The treatment and management of cerebral edema is among the duties of a neurointensivist. When and how to treat cerebral edema remain contentious. Further, a neurointensivist must remain cognizant of how their neurocentric therapies may affect the rest of the patient's body.

Research frontiers

Intravenous fluids and hypertonic saline are ubiquitous in the critical care and neurocritical care setting. Data has previously demonstrated "not all fluids are created equal." Understanding how the formulation of intravenous fluids may affect outcome is critical to providing effective critical care. Discovery of deleterious correlations may help generate prospective, hypothesis driven, studies on patient or disease specific intravenous fluids aimed at improving outcome.

Innovations and breakthroughs

Prior work has demonstrated that the formulation of hypertonic saline (HS) may not affect renal function. However, the relative change of Na^+, and presence in particular of hypernatremia, may correlate with development of kidney injury and worse outcomes. Much of this work was in a mixed critical care or mixed neurocritical care population. This study assessed if not only Na^+, but if Cl^-, HS formulation, and disease state played a role. The data here presented suggests potential rolls of Cl^- and disease state to adverse renal function. These findings need to be confirmed by larger, prospective trials. Potentially, such findings could form the basis for developing patient or disease specific intravenous fluids aimed at reducing cerebral edema and mitigating adverse renal effects. Further, if borne out in future studies, better understanding of what interactions occur between intravenous fluids, disease state, and comorbidities may allow for development of new therapeutic options in neurocritical care.

Applications

Data presented here, and in the context of literature to date, may suggest to the bedside clinician to be judicious with the prescription of HS to patients with cerebral edema, to closely monitor renal function, and use Cl^- limiting formulations of HS.

Terminology

Cerebral edema is the process whereby injured brain develops increase free water by cytotoxic or vasogenic means. Typically, these two pathologies combine in a temporal fashion. Much of the overall change of brain volume is related to this, a concern in the rigid volume provided within the skull. Potentially, cerebral edema may exacerbate inflammation. Hypertonic saline, or HS, are intravenous fluids of higher osmolarity aimed at increasing serum sodium. This has a multitude of effects including: (1) reducing brain free water and edema; (2) reducing aquaporin production and thus water entry into cells preventing/limiting the development of cerebral edema; (3) improving red blood cells malleability and ability to travel through injured tissue; and (4) potential mitigating effects on inflammation. Creatinine, Cr, is a biomarker of kidney health. Though crude, this is a readily available biomarker that can guide the clinicians management of a patient.

Peer review

This analysis provides some provocative findings that need a larger study to confirm. Further, it summarizes much of the literature on this topic to date.

REFERENCES

1 **Mayer SA**, Sacco RL, Shi T, Mohr JP. Neurologic deterioration in noncomatose patients with supratentorial intracerebral hemorrhage. *Neurology* 1994; **44**: 1379-1384 [PMID: 8058133]

2 **Kollmar R**, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke* 2010; **41**: 1684-1689

[PMID: 20616317 DOI: 10.1161/STROKEAHA.110.587758]
3 **Ropper AH**. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *N Engl J Med* 1986; **314**: 953-958 [PMID: 3960059]
4 **Ropper AH**, Shafran B. Brain edema after stroke. Clinical syndrome and intracranial pressure. *Arch Neurol* 1984; **41**: 26-29 [PMID: 6606414]
5 **Zazulia AR**, Diringer MN, Derdeyn CP, Powers WJ. Progression of mass effect after intracerebral hemorrhage. *Stroke* 1999; **30**: 1167-1173 [PMID: 10356094]
6 **Arima H**, Wang JG, Huang Y, Heeley E, Skulina C, Parsons MW, Peng B, Li Q, Su S, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Morgenstern LB, Chalmers J, Anderson CS. Significance of perihematomal edema in acute intracerebral hemorrhage: the INTERACT trial. *Neurology* 2009; **73**: 1963-1968 [PMID: 19996072 DOI: 10.1212/WNL.0b013e3181c55ed3]
7 **Thiex R**, Tsirka SE. Brain edema after intracerebral hemorrhage: mechanisms, treatment options, management strategies, and operative indications. *Neurosurg Focus* 2007; **22**: E6 [PMID: 17613237]
8 **Nau R**, Desel H, Lassek C, Thiel A, Schinschke S, Rössing R, Kolenda H, Prange HW. Slow elimination of mannitol from human cerebrospinal fluid. *Eur J Clin Pharmacol* 1997; **53**: 271-274 [PMID: 9476044]
9 **McGraw CP**, Howard G. Effect of mannitol on increased intracranial pressure. *Neurosurgery* 1983; **13**: 269-271 [PMID: 6413884]
10 **Vialet R**, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin C. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003; **31**: 1683-1687 [PMID: 12794404]
11 **Suarez JI**, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanley DF, Ulatowski JA. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med* 1998; **26**: 1118-1122 [PMID: 9635664]
12 **Strandvik GF**. Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure. *Anaesthesia* 2009; **64**: 990-1003 [PMID: 19686485 DOI: 10.1111/j.1365-044.2009.05986.x]
13 **Zeng HK**, Wang QS, Deng YY, Fang M, Chen CB, Fu YH, Jiang WQ, Jiang X. Hypertonic saline ameliorates cerebral edema through downregulation of aquaporin-4 expression in the astrocytes. *Neuroscience* 2010; **166**: 878-885 [PMID: 20083168 DOI: 10.1016/j.neuroscience.2009.12.076]
14 **Bulger EM**, May S, Brasel KJ, Schreiber M, Kerby JD, Tisherman SA, Newgard C, Slutsky A, Coimbra R, Emerson S, Minei JP, Bardarson B, Kudenchuk P, Baker A, Christenson J, Idris A, Davis D, Fabian TC, Aufderheide TP, Callaway C, Williams C, Banek J, Vaillancourt C, van Heest R, Sopko G, Hata JS, Hoyt DB. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. *JAMA* 2010; **304**: 1455-1464 [PMID: 20924011 DOI: 10.1001/jama.2010.1405]
15 **Aiyagari V**, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? *J Crit Care* 2006; **21**: 163-172 [PMID: 16769461]
16 **Huang PP**, Stucky FS, Dimick AR, Treat RC, Bessey PQ, Rue LW. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg* 1995; **221**: 543-554; discussion 554-557 [PMID: 7748036]
17 **Froelich M**, Ni Q, Wess C, Ougorets I, Härtl R. Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. *Crit Care Med* 2009; **37**: 1433-1441 [PMID: 19242317 DOI: 10.1097/CCM.0b013e31819c1933]
18 **Nin N**, Lombardi R, Frutos-Vivar F, Esteban A, Lorente JA, Ferguson ND, Hurtado J, Apezteguia C, Brochard L, Schortgen F, Raymondos K, Tomicic V, Soto L, González M, Nightingale P, Abroug F, Pelosi P, Arabi Y, Moreno R, Anzueto A. Early and small changes in serum creatinine concentrations are associated with mortality in mechanically ventilated patients. *Shock* 2010; **34**: 109-116 [PMID: 20634655 DOI: 10.1097/SHK.0b013e3181d671a6]
19 **Yahalom G**, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, Sela BA, Tanne D. Chronic kidney disease and clinical outcome in patients with acute stroke. *Stroke* 2009; **40**: 1296-1303 [PMID: 19182072 DOI: 10.1161/STROKEAHA.108.520882]
20 **Putaala J**, Haapaniemi E, Gordin D, Liebkind R, Groop PH, Kaste M, Tatlisumak T. Factors associated with impaired kidney function and its impact on long-term outcome in young ischemic stroke. *Stroke* 2011; **42**: 2459-2464 [PMID: 21737795 DOI: 10.1161/STROKEAHA.110.612721]
21 **Molshatzki N**, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, Tanne D. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. *Cerebrovasc Dis* 2011; **31**: 271-277 [PMID: 21178352 DOI: 10.1159/000322155]
22 **Rhoney DH**, Parker D, Millis SR, Whittaker P. Kidney dysfunction at the time of intracerebral hemorrhage is associated with increased in-hospital mortality: a retrospective observational cohort study. *Neurol Res* 2012; **34**: 518-521 [PMID: 22664363 DOI: 10.1179/1743132812Y.0000000041]
23 **Lin LC**, Yang JT, Weng HH, Hsiao CT, Lai SL, Fann WC. Predictors of early clinical deterioration after acute ischemic stroke. *Am J Emerg Med* 2011; **29**: 577-581 [PMID: 20825831 DOI: 10.1016/j.ajem.2009.12.019]
24 **Hao Z**, Wu B, Lin S, Kong FY, Tao WD, Wang DR, Liu M. Association between renal function and clinical outcome in patients with acute stroke. *Eur Neurol* 2010; **63**: 237-242 [PMID: 20332640 DOI: 10.1159/000285165]
25 **Zacharia BE**, Ducruet AF, Hickman ZL, Grobelny BT, Fernandez L, Schmidt JM, Narula R, Ko LN, Cohen ME, Mayer SA, Connolly ES. Renal dysfunction as an independent predictor of outcome after aneurysmal subarachnoid hemorrhage: a single-center cohort study. *Stroke* 2009; **40**: 2375-2381 [PMID: 19461033 DOI: 10.1161/STROKEAHA.108.545210]
26 **Misra UK**, Kalita J, Srivastava M, Mandal SK. Transient renal impairment in acute intracerebral haemorrhage. *J Neurol* 1996; **243**: 417-420 [PMID: 8741083]
27 **Li N**, Zhao WG, Zhang WF. Acute kidney injury in patients with severe traumatic brain injury: implementation of the acute kidney injury network stage system. *Neurocrit Care* 2011; **14**: 377-381 [PMID: 21298359 DOI: 10.1007/s12028-011-9511-1]
28 **Moore EM**, Bellomo R, Nichol A, Harley N, Macisaac C, Cooper DJ. The incidence of acute kidney injury in patients with traumatic brain injury. *Ren Fail* 2010; **32**: 1060-1065 [PMID: 20863210 DOI: 10.3109/0886022X.2010.510234]
29 http: //www.clinicaltrials.gov/ct2/show/study/NCT01605357?term=hypertonic saline&rank=72
30 http: //www.clinicaltrials.gov/ct2/show/NCT01215019?term=hypertonic saline&rank=84
31 **Diringer MN**, Scalfani MT, Zazulia AR, Videen TO, Dhar R, Powers WJ. Effect of mannitol on cerebral blood volume in patients with head injury. *Neurosurgery* 2012; **70**: 1215-1218; discussion 1219 [PMID: 22089753 DOI: 10.1227/NEU.0b013e3182417bc2]
32 **Wagner I**, Hauer EM, Staykov D, Volbers B, Dörfler A, Schwab S, Bardutzky J. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke* 2011; **42**: 1540-1545 [PMID: 21512173 DOI: 10.1161/STROKEAHA.110.609479]
33 **Rockswold GL**, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure,

and brain tissue oxygen. *Neurosurgery* 2009; **65**: 1035-1041; discussion 1041-1042 [PMID: 19934962 DOI: 10.1227/01.NEU.0000359533.16214.04]

34 **Al-Rawi PG**, Tseng MY, Richards HK, Nortje J, Timofeev I, Matta BF, Hutchinson PJ, Kirkpatrick PJ. Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. *Stroke* 2010; **41**: 122-128 [PMID: 19910550 DOI: 10.1161/STROKEAHA.109.560698]

35 **Nout YS**, Mihai G, Tovar CA, Schmalbrock P, Bresnahan JC, Beattie MS. Hypertonic saline attenuates cord swelling and edema in experimental spinal cord injury: a study utilizing magnetic resonance imaging. *Crit Care Med* 2009; **37**: 2160-2166 [PMID: 19487936 DOI: 10.1097/CCM.0b013e3181a05d41]

36 **Rizoli SB**, Rhind SG, Shek PN, Inaba K, Filips D, Tien H, Brenneman F, Rotstein O. The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. *Ann Surg* 2006; **243**: 47-57 [PMID: 16371736]

37 **Hatanaka E**, Shimomi FM, Curi R, Campa A. Sodium chloride inhibits cytokine production by lipopolysaccharide-stimulated human neutrophils and mononuclear cells. *Shock* 2007; **27**: 32-35 [PMID: 17172977]

38 **Ellis SJ**. Severe hyponatraemia: complications and treatment. *QJM* 1995; **88**: 905-909 [PMID: 8593551]

39 **Lenz K**, Gössinger H, Laggner A, Druml W, Grimm G, Schneeweiss B. Influence of hypernatremic-hyperosmolar state on hemodynamics of patients with normal and depressed myocardial function. *Crit Care Med* 1986; **14**: 913-914 [PMID: 3757536]

40 **Sakr Y**, Rother S, Ferreira AM, Ewald C, Dünisch P, Riedemmann N, Reinhart K. Fluctuations in serum sodium level are associated with an increased risk of death in surgical ICU patients. *Crit Care Med* 2013; **41**: 133-142 [PMID: 23128383 DOI: 10.1097/CCM.0b013e318265f576]

41 **Waite MD**, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. *J Crit Care* 2013; **28**: 405-412 [PMID: 23369520]

42 **Maggiore U**, Picetti E, Antonucci E, Parenti E, Regolisti G, Mergoni M, Vezzani A, Cabassi A, Fiaccadori E. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. *Crit Care* 2009; **13**: R110 [PMID: 19583864 DOI: 10.1186/cc7953]

43 **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]

44 **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]

45 **Wilcox CS**. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; **71**: 726-735 [PMID: 6826732]

46 **Pérez-Pérez AJ**, Pazos B, Sobrado J, Gonzalez L, Gándara A. Acute renal failure following massive mannitol infusion. *Am J Nephrol* 2002; **22**: 573-575 [PMID: 12381962]

47 **Gerber JG**, Branch RA, Nies AS, Hollifield JW, Gerkens JF. Influence of hypertonic saline on canine renal blood flow and renin release. *Am J Physiol* 1979; **237**: F441-F446 [PMID: 517657]

48 **Prowle JR**, Bellomo R. Fluid administration and the kidney. *Curr Opin Crit Care* 2010; **16**: 332-336 [PMID: 20543683 DOI: 10.1097/MCC.0b013e32833be90b]

49 **Scheingraber S**, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999; **90**: 1265-1270 [PMID: 10319771]

50 **Gazitúa S**, Scott JB, Chou CC, Haddy FJ. Effect of osmolarity on canine renal vascular resistance. *Am J Physiol* 1969; **217**: 1216-1223 [PMID: 5824323]

51 **Salomonsson M**, Gonzalez E, Kornfeld M, Persson AE. The cytosolic chloride concentration in macula densa and cortical thick ascending limb cells. *Acta Physiol Scand* 1993; **147**: 305-313 [PMID: 8386427]

52 **Bullivant EM**, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol* 1989; **256**: F152-F157 [PMID: 2912160]

53 **Udy A**, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M, Lipman J. Augmented creatinine clearance in traumatic brain injury. *Anesth Analg* 2010; **111**: 1505-1510 [PMID: 21048095 DOI: 10.1213/ANE.0b013e3181f7107d]

54 **Pelayo JC**. Renal adrenergic effector mechanisms: glomerular sites for prostaglandin interaction. *Am J Physiol* 1988; **254**: F184-F190 [PMID: 3125747]

55 **Hays AN**, Lazaridis C, Neyens R, Nicholas J, Gay S, Chalela JA. Osmotherapy: use among neurointensivists. *Neurocrit Care* 2011; **14**: 222-228 [PMID: 21153930 DOI: 10.1007/s12028-010-9477-4]

P- Reviewers: Duan SB, Makki N, Mitaka C **S- Editor**: Zhai HH
L- Editor: A **E- Editor**: Wu HL

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2014 August 4; 3(3): 68-73

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 3 Number 3 August 4, 2014

World Journal of Critical Care Medicine
Volume 3 Number 3 August 4, 2014

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

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

PUBLICATION DATE
August 4, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v3.i3.68

World J Crit Care Med 2014 August 4; 3(3): 68-73
ISSN 2220-3141 (online)

RETROSPECTIVE STUDY

French pre-hospital trauma triage criteria: Does the "pre-hospital resuscitation" criterion provide additional benefit in triage?

Emmanuel Hornez, Olga Maurin, Aurélie Mayet, Tristan Monchal, Federico Gonzalez, Delphine Kerebel

Emmanuel Hornez, Digestive Surgery, Percy Military Hospital, 92140 Clamart, France
Emmanuel Hornez, Service de Chirurgie Thoracique et Viscérale, Hôpital d'Instruction des Armées PERCY, 92140 Clamart, France
Olga Maurin, Medical Service, Fire Department, 75012 Paris, France
Aurélie Mayet, Department of Epidemiology, Health Service, French Armed Forces, 13000 Marseille, France
Tristan Monchal, Digestive Surgery, Sainte Anne Military Hospital, 83000 Toulon, France
Federico Gonzalez, Digestive Surgery, Percy Military Hospital, French Armed Forces, 92140 Clamart, France
Delphine Kerebel, Emergency Department, Sainte Anne Military Hospital, 83000 Toulon, France
Author contributions: Hornez E contributed to the study conception and design; Maurin O and Kerebel D contributed to the acquisition of data; Hornez E, Mayet A and Monchal T contributed to the analysis and interpretation of data; Hornez E and Gonzalez F contributed to the drafting of manuscript; Gonzalez F contributed to critical revision.
Correspondence to: Emmanuel Hornez, MD, Service de Chirurgie Thoracique et Viscérale, Hôpital d'Instruction des Armées PERCY, 101 Avenue Henri Barbusse, 92140 Clamart, France. emmanuelhornez@free.fr
Telephone: +33-14-1466167 Fax: +33-14-1466169
Received: April 7, 2014 Revised: June 21, 2014
Accepted: July 25, 2014
Published online: August 4, 2014

Abstract

AIM: To evaluate the performance of the specific French Vittel "Pre-Hospital (PH) resuscitation" criteria in selecting polytrauma patients during the pre-hospital stage and its potential to increase the positive predictive value (PPV) of pre-hospital trauma triage.

METHODS: This was a monocentric prospective cohort study of injured adults transported by emergency medical service to a trauma center. Patients who met any of the field trauma triage criteria were considered "triage positive". Hospital data was statistically linked to pre-hospital records. The primary outcome of defining a "major trauma patient" was Injury Severity Score (ISS) > 16.

RESULTS: There were a total of 200 injured patients evaluated over a 2 years period who met at least 1 triage criterion. The number of false positives was 64 patients (ISS < 16). The PPV was 68%. The sensitivity and the negative predictive value could not be evaluated in this study since it only included patients with positive Vittel criteria. The criterion of "PH resuscitation" was present for 64 patients (32%), but 10 of them had an ISS < 16. This was statistically significant in correlation with the severity of the trauma in univariate analysis (OR = 7.2; P = 0.005; 95%CI: 1.6-31.6). However, despite this correlation the overall PPV was not significantly increased by the use of the criterion "PH resuscitation" (68% *vs* 67.8%).

CONCLUSION: The criterion of "pre-hospital resuscitation" was statistically significant with the severity of the trauma, but did not increase the PPV. The use of "pre-hospital resuscitation" criterion could be re-considered if these results are confirmed by larger studies.

Key words: Pre-hospital; Triage; Vittel criteria; Injury Severity Score; Trauma

Core tip: This is the first evaluation of French Vittel criteria for pre hospital triage of trauma. The results of this study suggest that the criteria are efficient to select the severe trauma patients during the pre-hospital stage [positive predictive value (PPV) of 68%]. The criterion "pre-hospital resuscitation" was significantly correlated with the severity of the trauma, but did not

increase the PPV. This criterion, which is the only difference between French and United Stated pH triage criteria, does not procure extra value and compromises potential comparisons with multinational cohort studies. The use of "pre-hospital resuscitation" criterion should be revaluated if these results are confirmed by larger studies.

Hornez E, Maurin O, Mayet A, Monchal T, Gonzalez F, Kerebel D. French pre-hospital trauma triage criteria: Does the "pre-hospital resuscitation" criterion provide additional benefit in triage? *World J Crit Care Med* 2014; 3(3): 68-73 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i3/68.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i3.68

INTRODUCTION

The ideal pre-hospital (PH) triage should optimize the resources in a trauma center or in local hospitals by restricting over- and undertriage scenarios, thereby limiting undue costs and unnecessary geographical constraints for patients and families. Since 1987, a regularly updated PH triage scheme has been prepared by the American College of Surgeons Committee on Trauma (ACSCOT)[1]. This scheme includes mechanism of injuries and replaces previously ineffective scoring such as trauma score[2,3], trauma triage rule[4], CRAM scale[5] and the PH index[6].

French PH trauma triage criteria were developed during the 2002 Emergency Ambulance Service (SAMU) conference in Vittel (France), which addressed French specific PH care[7]. Triage criteria are classified into 5 categories and each of the criteria is sufficient to define a severe trauma, indicating the transfer of the patient to a trauma center. The Vittel criteria are similar to the ACSCOT classification with an additional criterion: "PH resuscitation" which corresponds to the specific management provided by the PH emergency physician (PHEP).

This study aims at evaluating whether the "PH resuscitation" criterion increases the positive predictive value (PPV) of Vittel criteria for an adult population. The study hypothesis is that the PPV is not increased, considering that all of the PH resuscitation maneuvers would be based on vital signs criteria, which are already factored into the triage assessment.

MATERIALS AND METHODS

Study design

This monocentric study compares the PH Vittel criteria (Table 1) with 2 scores calculated at the end of the clinical assessment: the Injury Severity Score (ISS) and the Trauma Injury Severity Score (TRISS). Polytrauma was defined as an ISS > 16. The goal of the study was to evaluate the performance of Vittel criteria to select polytrauma patients during the pre-hospital stage and evaluate any additional benefit with the use of the specific criterion "PH resuscitation". The data was prospectively collected. The protocol was approved by the Institutional Review Board.

Table 1 Vittel pre-hospital triage criteria[1]

Steps	Severity criteria
1 Vital signs	Glasgow coma scale < 13 or Systolic blood pressure < 90 mmHg or Saturation O2 < 90%
2 Evidence of high-energy trauma	Ejection from automobile Death in same passenger compartment Falls > 6 m Victim thrown or crushed Global assessment of the trauma (aspect of the crashed vehicle, vehicle telemetry data consistent with high risk of injury, no motorcycle helmet, no seat belt) Blast
3 Anatomy of injury	Penetrating trauma of head, neck thorax, abdomen, pelvis, thigh, and arm Flail chest Severe burns, smoke inhalation Pelvic bone fracture Suspicion of medullar trauma Amputation proximal to wrist or ankle Acute ischemia of the limb
4 Pre-hospital resuscitation	Intubated and mechanically ventilated patients IV Fluids > 1000 mL (colloids) Catecholamine Anti-shock trousers inflated
5 Special patient or system considerations	Age > 65 yr Heart failure Respiratory failure Pregnancy > 12 wk

[1]The patient is considered as a severe trauma if he met one of the listed criteria and transferred to a trauma center.

Patient selection

From December 2008 to January 2010, all trauma patients were evaluated by the emergency physician in the field. The number of positive Vittel criteria was determined from the trauma case history including the phone report to the emergency department (ED). Patients presenting with one positive Vittel criterion were transported to and managed in a well equipped trauma center with an emergency department, intensive care unit, interventional radiology, a burn unit, and multiple surgical specialties (digestive, orthopedics, urology, otorhinolaryngology, plastic/reconstructive, neurosurgery). The facility receives an annual patient population of 900000, primarily tourists as well as residents of suburban and rural neighborhoods.

Data collected

The pre-defined data sheet utilized was divided into 2 parts: (1) collected PH stage data: Glasgow coma scale, respiratory rate, blood pressure, heart rate, injury mechanism, time of management, Vittel criteria, resuscitation protocol (IV fluids, oral intubation, venous access, drugs); (2) collected ED data: vitals, resuscitation protocol, injury profile, surgery, interventional radiology, survey, cause of death. ISS and TRISS were calculated at patient discharge.

Table 2 Profile of injury

Mechanism	*n* (%)	
Motorcycle crash	105 (52.7)	
Car crash	37 (18.5)	
Fall	30 (15.8)	
Pedestrian *vs* auto	16 (8)	
Gunshot wound	5 (2.5)	
Stab wound	2 (1)	
Other	4 (2)	
Anatomy of injury		
	Total *n* (%)	Hemorragic group *n* (%)
Number	200	33 (16.5)
Extremity		
Upper	60 (30)	8 (24)
Lower	53 (26.5)	9 (28)
Thorax		
Lung trauma	39 (19.5)	3 (9)
Pneumothorax	29 (14.5)	4 (12)
Hemothorax	21 (10.5)	14 (42.5)
Head	97 (48.5)	14 (42.5)
Face	39 (19.5)	4 (12)
Spine		
Stable	29 (14.5)	4 (12)
Unstable	8 (4)	0
Pelvic bone		
Stable	26 (13)	4 (12)
Unstable	10 (5)	6 (18)
Abdomen		
Hemoperitoneum	31 (15.5)	17 (51.5)
Hemoretroperitoneum	13 (6.5)	6 (18)
Pneumoperitoneum	3 (1.5)	1 (3)
Other	3 (1.5)	1 (3)

Statistical analysis

A statistical analysis evaluated the performance of the Vittel criteria in selecting patients with an ISS > 16 (Stata version 9 software, Stata Corporation). A descriptive analysis with the comparison between the subgroups was made with ANOVA. The correlation between the variables utilized the Pearson coefficient. Linear regression, univariate and multivariate analysis were used to measure the link between Vittel criteria and the ISS and TRISS. The significance level of the study was Ⅲ.

RESULTS

Population

Two hundred trauma patients (using Vittel criteria) were included. Characteristics and profiles of injuries are described in Table 2. The median age was 40.4 years (with range of 16-96 years) and 78.5% of patients were male. All traumas were high energy (road trauma 71%, serious falls 15%). The median values of ISS and TRISS were respectively 22 (1-75, EC = 16.1) and 95.8% (2-99, EC = 29). As expected, the 2 scores had a high inverse correlation (ρ = -0.77). Forty-four percent of patients were hemodynamically unstable, 48.5% had limb trauma, head trauma 48.5%, and thoracic trauma 44.5%. The most common injury involved trauma of the extremities (48.5%), then head trauma (48.5%), and thoracic trauma (44.5%). The severity of trauma did not vary with gender.

Table 3 Correlation between the severity of trauma[1] and positive Vittel criteria

Vittel Criteria	Univariate analysis			Multivariate analysis		
	OR	*P*	95%CI	OR	*P*	95%CI
Vital signs	2.8	0.002	1.4-5.3	2.4	0.04	1.0-5.7
Evidence of high-energy trauma	1	0.8	0.5- 2.4	1.2	0.64	0.5-3.1
Anatomy of injury	0.6	0.2	0.2-1.4	0.5	0.21	0.2-1.5
Pre-hospital resuscitation	2.6	0.005	1.3-5.0	1.8	0.18	0.7-4.4
Special patient or system considerations	7.2	0.009	1.6-31.6	9.2	0.004	2.0-41.9

[1]ISS > 16.

The elderly patients had a lower TRISS (P = 0.002) but with an unchanged ISS (P = 0.118). No mechanism was associated with a high ISS. Gunshot-penetrating trauma could be associated with a lower TRISS (P = 0.06).

PH stage

All patients were managed by a PHEP on the field. The median PH duration was 64.9 min (DS = 41.7 min, 15-240). This duration was associated with a lower TRISS (P = 0.015) but not with a higher ISS (P = 0.075). The first PHEP clinical report by phone and the first ED categorization of the patient were highly correlated (P = 0.88).

Analysis of the Vittel criteria

The number of false positives was 64 patients (ISS < 16 and at least one positive Vittel criteria). The PPV was 68%. The PPV was not significantly increased with the use of the criterion "PH resuscitation" (68% *vs* 67.8%). The sensitivity and the negative predictive value could not be evaluated in this study since it only included patients with positive Vittel criteria.

The distribution of the Vittel criteria is depicted in Figure 1. The most frequent criteria were "high energy trauma" (84.5%), and "physiological variables" (37%). Forty-eight percent of the patients had only one positive criterion; 23%, 23.5% and 3% had respectively 2, 3 and 4 positive criteria. No patient had 5 positive criteria.

The correlation between the positive Vittel criteria and the severity is detailed in Table 3. In univariate analysis, 3 criteria were associated with severity: "Vital signs" (OR = 2.8; P = 0.002; 95%CI: 1.4-5.3), "PH resuscitation" (OR = 7.2; P = 0.005; 95%CI: 1.6-31.6), and "Special patient or system consideration" (OR = 7.2; P = 0.009; OR = 1.6-31.6). In multivariate analysis, 2 criteria were associated with the severity: "vital signs" (OR = 2.4; P = 0.04; 95%CI: 1.0-5.7) and "Special patient or system consideration" (OR = 9.2; P = 0.004; 95%CI: 2.0-41.9). For the entire cohort: The more a patient had positive criteria, the more severe the trauma (P < 0.0001) and the more the patient needed emergency surgery (not statistically significant). For the group of "hemorrhagic patients": the more a patient had positive criteria, the more severe the trauma (not statistically significant) and the more the patient needed an emer-

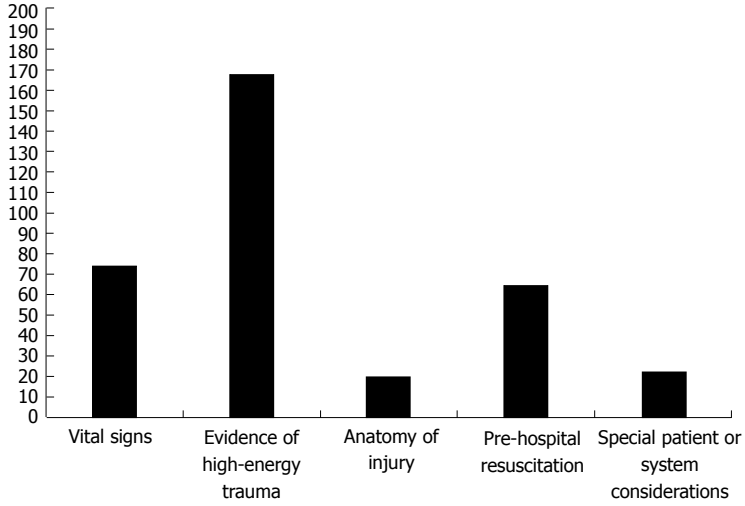


Figure 1 Distribution of positive Vittel criteria.

gency surgery (significant with regression analysis).

DISCUSSION

This study was intended to evaluate if the "PH resuscitation" criterion increases the PPV of Vittel criteria for an adult population. The study hypothesis was that the PPV is not increased, considering that all of the PH resuscitation maneuvers would presumably be based on vital sign criteria, which would then already be factored into the triage assessment. The results suggest that the French Vittel criteria are effective in selecting polytrauma patients (ISS > 16) with a PPV of 68%. The criterion of "PH resuscitation" does not improve the performance of the Vittel criteria.

Definition

There is no consensus for the definition of polytrauma; many definitions have been used: ISS > 16[8-12], ISS > 20[13], ISS > 16 associated with hospital length[14], ISS associated with resources used[8,15,16]. Other studies define polytrauma depending on the resources used[4,17-20]. In this study we used the definition of the ACSCOT (ISS > 16). This definition optimizes the cost/efficiency ratio of the trauma centers[21].

Overall Vittel criteria performance

In Westernized countries, severe trauma patients are usually identified during the PH stage by triage criteria as the "ACSCOT field triage decision scheme", the last version published in 2006. Many studies have since been published to evaluate the triage criteria, with varying results[8,21-25]. In 2011, Newgard *et al*[23] published a major study about pre-hospital triage. In the study, 122345 patients were included and 7100 (5.8%) had an ISS > 16. The pre-hospital triage was done by the paramedics using the ACSCOT scheme. The sensitivity was 85% for all patients and 79% for patients over 55 years of age. The specificity was 68.7% for all the patients and 75.4% for patients older than 55 years. The PPV to identify major trauma patients was 71.1%.

In France, the PH management of a trauma patient is performed by a mobile team including a PHEP. PHEP field management includes Cardio Pulmonary resuscitation with oral intubation, PRBC transfusion, chest tube, central venous access, and/or Fast Assessment Sonogram for Trauma exam. Therefore, specific criteria for pre-hospital triage have been published in 2002 during the SAMU conference in Vittel[7] and are summarized in table 1. These are very similar to those of the ACSCOT, but also include the additional criterion of "PH resuscitation". As expected, the performance of the Vittel criteria to identify polytrauma is very similar to the ACSCOT score (PPV: 68% *vs* 71.1%).

Performance of the criterion "PH resuscitation"

In this study, the criterion "PH resuscitation" was met by 64 patients (32%) but 10 of them had an ISS < 16. The false positive rate was 15%. This was significantly correlated with the severity of the trauma in univariate analysis (OR = 7.2; P = 0.005; 95%CI: 1.6-31.6). However, despite this correlation, the overall PPV was not significantly increased by the use of the criterion "PH resuscitation" (68% *vs* 67.8%)

Performance of the other criteria

Criterion "Vital signs": In this study, the criterion "Vital signs" was significantly associated with the severity of the trauma in univariate analysis (OR = 2.8; P = 0.002; 95%CI: 1.4-5.3) and multivariate analysis (OR = 2.4; P = 0.04; 95%CI: 1.0-5.7). The effectiveness of this criterion was already discovered by Wuerz *et al*[24], in 1996, with a low sensitivity (56%) but a high specificity (86%). This was associated with 20% mortality rate in the study published in 2005 by Hannan *et al*[26].

Criterion "evidence of high-energy trauma": In this study, the criterion "evidence of high-energy trauma" was not correlated with the severity of the trauma in the uni-

variate or multivariate analysis. Many studies have already shown that the mechanism of trauma is not associated with the severity of trauma[10,13,27,28]. In a study published in 1986, Lowe *et al*[27] found an overtriage rate ranging from 14% to 43% in a cohort of 631 patients. This trend was corroborated in 2003 by Santaniello *et al*[28]. In a series of 830 patients, only 50% of the patients sorted by this criterion required surgery or an ICU admission. This criterion presents an element of sensitivity for the PH triage.

Criterion "anatomy of injury": In this study, the criterion 'anatomy of injury' was not correlated with the severity of the trauma. Few studies have specifically analyzed this criterion: in 1995 Cooper *et al*[8] found a sensitivity of 40% with a PPV of 22%.

Criterion "Special patient or system considerations": Within the study the criterion "Special patient or system considerations" was significantly associated with the severity of the trauma in univariate analysis (OR = 7.2; P = 0.009; 95%CI: 1.6-31.6) and multivariate analysis (OR = 9.2; P = 0.004; 95%CI: 2.0-41.9), but an accurate analysis of this criterion is difficult due to its variability (its contents being extremely PHEP dependent). It is however interesting to notice, that the specificity of the triage was higher for the patient older than 55 years (75.4% *vs* 64.3%) in the study of the ACSCOT[23].

Limitations

The limitations of this study include a lack of statistical power due to the small cohort size. Also, we only included patients with one or more positive Vittel criteria, therefore we could not adequately assess the sensitivity of the criteria, which is the largest limitation. In addition, while the number of positive criteria was significantly associated with the severity of the trauma, this relationship did not exist with the subgroup "hemorrhagic patients" despite a hemorrhagic lesion being a severity factor in trauma, as shown by the higher need of emergency surgery. This paradox is probably due to a lack of statistical power due to the small cohort of hemorrhagic patients (n = 33). A larger study size is needed.

Overall, the results of this study indicate that the French Vittel criteria are efficient in selecting severe trauma patients during the pre-hospital stage, with a PPV of 68%. The criterion "pre-hospital resuscitation" was significantly correlated with the severity of the trauma, but did not increase the PPV. This criterion, which is the only difference between the French and the United States PH triage criteria, does not provide any added benefit, and actually compromises potential comparisons with multinational cohort studies. The use of "pre-hospital resuscitation" criterion should be re-evaluated if these results are confirmed by larger studies.

COMMENTS

Background

A pre-hospital (PH) triage is performed to optimize the resources in a trauma center or in local hospitals by restricting over- and undertriage scenarios. Since 1987, a regularly updated PH triage scheme has been prepared by the American College of Surgeons Committee on Trauma (ACSCOT). This scheme includes mechanism of injuries. French PH trauma triage criteria were developed in 2002. They are similar to the ACSCOT classification with an additional criterion: "PH resuscitation" which corresponds to the specific management provided by the PH emergency physician.

Innovations and breakthroughs

This article is the first evaluation of the French triage criteria. They are no related or similar studies. A larger study will be performed by the emergency health service in Paris in 2015.

Applications

The results of this study indicate that the French Vittel criteria are efficient in selecting severe trauma patients during the pre-hospital stage, with a PPV of 68% but the criterion "pre-hospital resuscitation" did not increase the PPV. This criterion does not provide any added benefit, and actually compromises potential comparisons with multinational studies. This study is a clear advocacy for reconsidering the use this criterion if these results are confirmed by larger studies.

Peer review

The authors performed a monocentric prospective cohort study of injured adults to evaluate the performance of the French Vittel criteria to select polytrauma patients during pre-hospital stage and evaluate if their pre hospital resuscitation criterion increases positive predictive value of pre-hospital trauma triage.

REFERENCES

1 Hospital and prehospital resources for optimal care of the injured patient. Committee on Trauma of the American College of Surgeons. *Bull Am Coll Surg* 1986; **71**: 4-23 [PMID: 10278815]

2 **Gennarelli TA**, Champion HR, Sacco WJ, Copes WS, Alves WM. Mortality of patients with head injury and extracranial injury treated in trauma centers. *J Trauma* 1989; **29**: 1193-1201; discussion 1201-1202 [PMID: 2769804 DOI: 10.1097/00005373-198909000-00002]

3 **Moreau M**, Gainer PS, Champion H, Sacco WJ. Application of the trauma score in the prehospital setting. *Ann Emerg Med* 1985; **14**: 1049-1054 [PMID: 3931510 DOI: 10.1016/S0196-0644(85)80917-3]

4 **Baxt WG**, Jones G, Fortlage D. The trauma triage rule: a new, resource-based approach to the prehospital identification of major trauma victims. *Ann Emerg Med* 1990; **19**: 1401-1406 [PMID: 2240753 DOI: 10.1016/S0196-0644(05)82608-3]

5 **Gormican SP**. CRAMS scale: field triage of trauma victims. *Ann Emerg Med* 1982; **11**: 132-135 [PMID: 7065486 DOI: 10.1016/S0196-0644(82)80237-0]

6 **Koehler JJ**, Baer LJ, Malafa SA, Meindertsma MS, Navitskas NR, Huizenga JE. Prehospital Index: a scoring system for field triage of trauma victims. *Ann Emerg Med* 1986; **15**: 178-182 [PMID: 3946860 DOI: 10.1016/S0196-0644(86)80016-6]

7 **Riou B**, Thicoïpé M, Atain-Kouadio P, Carli P. Comment évaluer la gravité ? In : Samu de France. Actualités en réanimation préhopistalière : le traumatisé grave. Paris : SFEM éditions, 2002: 115-118

8 **Cooper ME**, Yarbrough DR, Zone-Smith L, Byrne TK, Norcross ED. Application of field triage guidelines by pre-hospital personnel: is mechanism of injury a valid guideline for patient triage? *Am Surg* 1995; **61**: 363-367 [PMID: 7893107]

9 **Esposito TJ**, Offner PJ, Jurkovich GJ, Griffith J, Maier RV. Do prehospital trauma center triage criteria identify major trauma victims? *Arch Surg* 1995; **130**: 171-176 [PMID: 7848088 DOI: 10.1001/archsurg.1995.01430020061010]

10 **Knopp R**, Yanagi A, Kallsen G, Geide A, Doehring L. Mechanism of injury and anatomic injury as criteria for prehospital trauma triage. *Ann Emerg Med* 1988; **17**: 895-902 [PMID: 3415061 DOI: 10.1016/S0196-0644(88)80666-8]

11 **Long WB**, Bachulis BL, Hynes GD. Accuracy and relationship of mechanisms of injury, trauma score, and injury severity score in identifying major trauma. *Am J Surg* 1986; **151**:

581-584 [PMID: 3706634 DOI: 10.1016/0002-9610(86)90553-2]
12 **Bond RJ**, Kortbeek JB, Preshaw RM. Field trauma triage: combining mechanism of injury with the prehospital index for an improved trauma triage tool. *J Trauma* 1997; **43**: 283-287 [PMID: 9291374 DOI: 10.1097/00005373-199708000-00013]
13 **Cottington EM**, Young JC, Shufflebarger CM, Kyes F, Peterson FV, Diamond DL. The utility of physiological status, injury site, and injury mechanism in identifying patients with major trauma. *J Trauma* 1988; **28**: 305-311 [PMID: 3351989 DOI: 10.1097/00005373-198803000-00005]
14 **West JG**, Murdock MA, Baldwin LC, Whalen E. A method for evaluating field triage criteria. *J Trauma* 1986; **26**: 655-659 [PMID: 3723642]
15 **Newgard CD**, Hui SH, Griffin A, Wuerstle M, Pratt F, Lewis RJ. Prospective validation of an out-of-hospital decision rule to identify seriously injured children involved in motor vehicle crashes. *Acad Emerg Med* 2005; **12**: 679-687 [PMID: 16079420 DOI: 10.1197/j.aem.2005.03.526]
16 **Simon BJ**, Legere P, Emhoff T, Fiallo VM, Garb J. Vehicular trauma triage by mechanism: avoidance of the unproductive evaluation. *J Trauma* 1994; **37**: 645-649 [PMID: 7932897]
17 **Henry MC**, Hollander JE, Alicandro JM, Cassara G, O' Malley S, Thode HC. Incremental benefit of individual American College of Surgeons trauma triage criteria. *Acad Emerg Med* 1996; **3**: 992-1000 [PMID: 8922003 DOI: 10.1111/j.1553-2712.1996.tb03340.x]
18 **Zechnich AD**, Hedges JR, Spackman K, Jui J, Mullins RJ. Applying the trauma triage rule to blunt trauma patients. *Acad Emerg Med* 1995; **2**: 1043-1052 [PMID: 8597914 DOI: 10.1111/j.1553-2712.1995.tb03148.x]
19 **Phillips JA**, Buchman TG. Optimizing prehospital triage criteria for trauma team alerts. *J Trauma* 1993; **34**: 127-132 [PMID: 8437179]
20 **Engum SA**, Mitchell MK, Scherer LR, Gomez G, Jacobson L, Solotkin K, Grosfeld JL. Prehospital triage in the injured pediatric patient. *J Pediatr Surg* 2000; **35**: 82-87 [PMID: 10646780 DOI: 10.1016/S0022-3468(00)80019-6]
21 **MacKenzie EJ**, Weir S, Rivara FP, Jurkovich GJ, Nathens AB, Wang W, Scharfstein DO, Salkever DS. The value of trauma center care. *J Trauma* 2010; **69**: 1-10 [PMID: 20622572]
22 **van Laarhoven JJ**, Lansink KW, van Heijl M, Lichtveld RA, Leenen LP. Accuracy of the field triage protocol in selecting severely injured patients after high energy trauma. *Injury* 2014; **45**: 869-873 [PMID: 24472800 DOI: 10.1016/j.injury.2013.12.010]
23 **Newgard CD**, Zive D, Holmes JF, Bulger EM, Staudenmayer K, Liao M, Rea T, Hsia RY, Wang NE, Fleischman R, Jui J, Mann NC, Haukoos JS, Sporer KA, Gubler KD, Hedges JR. A multisite assessment of the American College of Surgeons Committee on Trauma field triage decision scheme for identifying seriously injured children and adults. *J Am Coll Surg* 2011; **213**: 709-721 [PMID: 22107917 DOI: 10.1016/j.jamcollsurg.2011.09.012]
24 **Wuerz R**, Taylor J, Smith JS. Accuracy of trauma triage in patients transported by helicopter. *Air Med J* 1996; **15**: 168-170 [PMID: 10162103 DOI: 10.1016/S1067-991X(96)90025-5]
25 **Báez AA**, Lane PL, Sorondo B. System compliance with out-of-hospital trauma triage criteria. *J Trauma* 2003; **54**: 344-351 [PMID: 12579063]
26 **Hannan EL**, Farrell LS, Cooper A, Henry M, Simon B, Simon R. Physiologic trauma triage criteria in adult trauma patients: are they effective in saving lives by transporting patients to trauma centers? *J Am Coll Surg* 2005; **200**: 584-592 [PMID: 15804473 DOI: 10.1016/j.jamcollsurg.2004.12.016]
27 **Lowe DK**, Oh GR, Neely KW, Peterson CG. Evaluation of injury mechanism as a criterion in trauma triage. *Am J Surg* 1986; **152**: 6-10 [PMID: 3728819]
28 **Santaniello JM**, Esposito TJ, Luchette FA, Atkian DK, Davis KA, Gamelli RL. Mechanism of injury does not predict acuity or level of service need: field triage criteria revisited. *Surgery* 2003; **134**: 698-703; discussion 703-704 [PMID: 14605632 DOI: 10.1016/S0039-6060(03)00331-3]

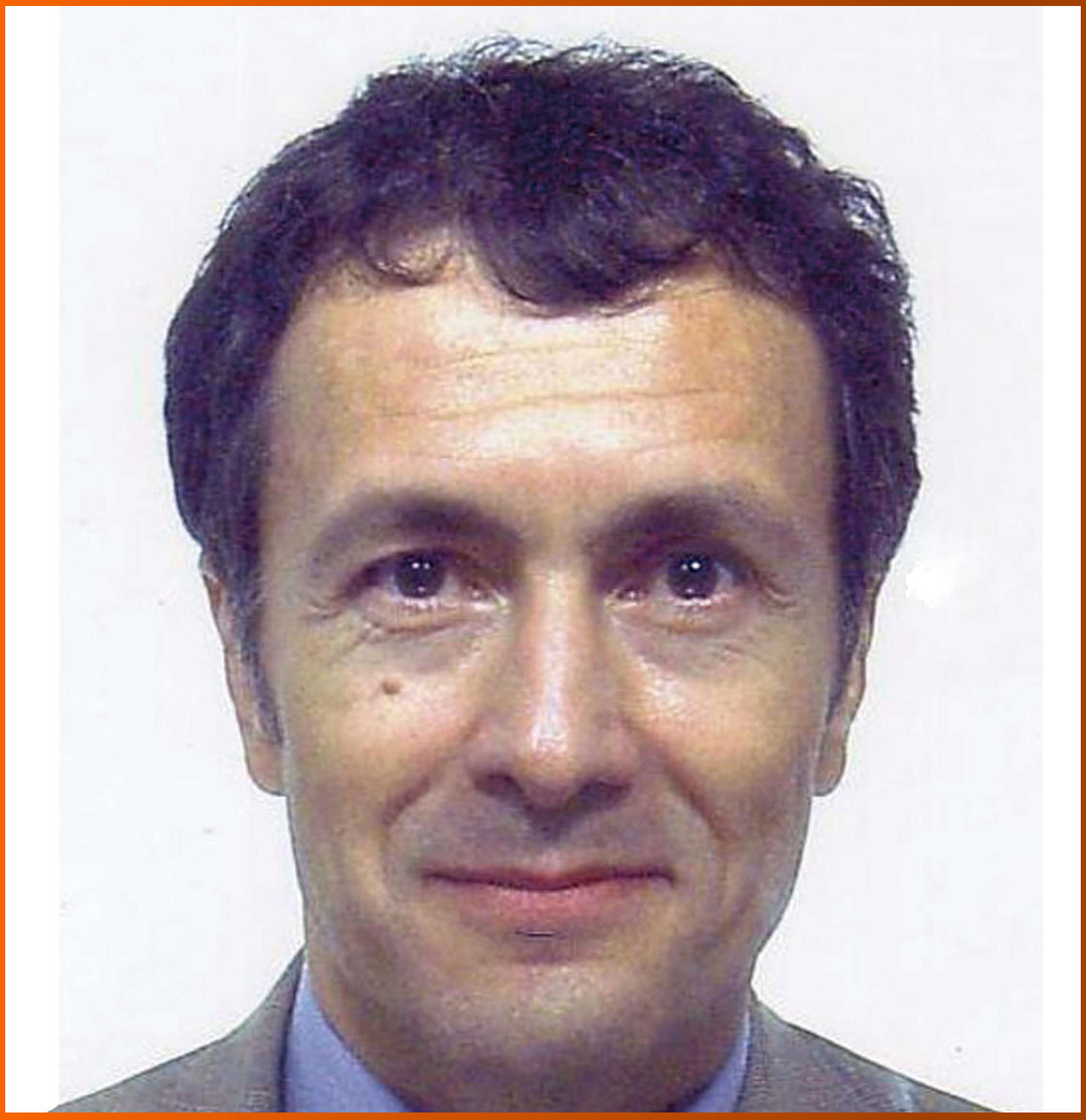
P- Reviewer: Moghazy A, Sadoghi P **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu HL

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2014 November 4; 3(4): 74-112

Volume End



Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 3 Number 4 November 4, 2014

World Journal of Critical Care Medicine
Volume 3 Number 4 November 4, 2014

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

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

PUBLICATION DATE
November 4, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v3.i4.74

World J Crit Care Med 2014 November 4; 3(4): 74-79
ISSN 2220-3141 (online)

EDITORIAL

Intensive care performance: How should we monitor performance in the future?

Tim K Timmers, Michiel HJ Verhofstad, Karl GM Moons, 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
Karl GM Moons, Department of Clinical Epidemiology, Julius Centre for Health Sciences and Primary Care, 3508 GA Utrecht, The Netherlands
Author contributions: All the authors contributed to this paper.
Correspondence to: Tim K Timmers, MD, PhD, Department of Surgery, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. tk.timmers@gmail.com
Telephone: +31-88-7559882 Fax: +31-88-7555555
Received: June 10, 2014 Revised: September 24, 2014
Accepted: October 14, 2014
Published online: November 4, 2014

Abstract

Intensive care faces economic challenges. Therefore, evidence proving both effectiveness and efficiency, *i.e.*, cost-effectiveness, of delivered care is needed. Today, the quality of care is an important issue in the health care debate. How do we measure quality of care and how accurate and representative is this measurement? In the following report, several topics which are used for the evaluation of intensive care unit (ICU) performance are discussed: (1) The use of general outcome prediction models to determine the risk of patients who are admitted to ICUs in an increasing variety of case mix for the different intensive care units, together with three major limitations; (2) As critical care outcomes research becomes a more established entity, mortality is now only one of many endpoints that are relevant. Mortality is a limited outcome when assessing critical care performance, while patient interest in quality of life outcomes is relevant; and (3) The Quality Indicators Committee of the Society of Critical Care Medicine recommended that short-term readmission is a major performance indicator of the quality of intensive care medicine.

Key words: Intensive care performance; Quality of care; Critical care; Intensive care medicine

Core tip: Variations in case mix, intensive care unit (ICU) demographics, clinical and non-clinical factors not addressed by the present severity of illness scores must be quantified to improve the accuracy of future prediction models. A completely different benefit using health-related quality of life (HrQoL) as a performance benchmark could be the follow-up evaluation of the patient's health status after ICU or hospital discharge. The moment when outcome research can predict the short-term (ICU discharge) QoL of a critically ill patient during the first 24 h of ICU admission will give physicians and health care policy makers an up-to-date and reliable evaluation of quality of care in the ICU for the future.

Timmers TK, Verhofstad MHJ, Moons KGM, Leenen LPH. Intensive care performance: How should we monitor performance in the future? *World J Crit Care Med* 2014; 3(4): 74-79 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i4/74.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i4.74

INTRODUCTION

The intensive care unit (ICU) is a hospital unit delivering continuous surveillance and highly specialized care to critically ill patients, either medical or surgical. Patients' conditions are life-threatening and require comprehensive care[1]. Established approximately five decades ago, the ICU is now a fundamental part of hospital care. It presents itself as the knowledge that aims to help patients with extended needs of care and organ support[2].

Intensive care faces economic challenges. Therefore, evidence proving both effectiveness and efficiency, *i.e.*,

cost-effectiveness, of delivered care is needed. ICUs consume a significant proportion of health care resources, accounting for up to 20% of a hospital's cost[3-8]. By 2005, critical care medicine costs in the United States were estimated to be $81.7 billion, accounting for 4.1% of the national health expenditures and 0.66% of the gross domestic product[9]. The United States spends 15% of the gross domestic product on health care (9%-11% in Germany, France and Canada; 7%-8% in Spain and the United Kingdom). Intensive care costs are estimated to be increasing throughout the developed world[4,7,10-17].

Today, quality of care is an important issue in the health care debate[18]. All countries struggle to optimize quality of care while minimizing costs. Assessment of clinical performance is obligatory for the evaluation of both the effectiveness and efficiency of care[19] and therefore several questions arise: How do we measure quality of care and how accurate and representative is this measurement?

The goal of intensive care medicine is to achieve the best outcome for critically ill patients and this is usually accompanied by the use of very complex care[2,20]. All patients carry both an intrinsic (disease-related) and an extrinsic (care-related) risk at the same time[2,21]. There is an ever-increasing acknowledgement of the wide variation in the quality of care across ICUs and its effect on outcome. Indicators to evaluate the quality of care are progressively being used and focus on patient outcome[18,22]. Finding a solid technique to determine the performance of single ICUs has been a difficult pursuit for the last 30 years[19].

OUTCOME PREDICTION MODELS: SHALL WE CONTINUE IN THE SAME WAY?

Each new development in critical care treatment over the past 30 years has been implemented to improve the quality of care. Therefore, the extrinsic risks that patients carry should be as low as possible. Ideally, quality of care performance research should give more information about the extrinsic rather than the intrinsic risks. Presently, ICU performance evaluation is becoming increasingly difficult because of the presence of an increasing variety in patient case mix for the different intensive care units. Since the development of prediction mortality models in the early 1980s, physicians have tried to normalize certain ICU populations through the use of severity of illness measurements. At the time that a general outcome prediction model (GOPM) was developed, the intrinsic risk had been adjusted in such a way that performance mainly illuminated the extrinsic risk factors. Most published approaches concerning the evaluation of ICU performance adopt more or less identical methods: the development of a GOPM and its calibration in a suitable database. Such models are then applied to different cohorts of ICU patients and the comparison of the predicted number of deaths with the actual number is used as a reference for the clinical behavior of the unit[15]. For over 30 years, outcome research in critical care relied heavily on these risk adjustment methods (GOPM) to assess and quantify the risk of patients admitted to ICUs[2]. Using several GOPMs, this methodology has become the "gold standard" to compare ICUs across different geographical areas or within a specific individual nation or other specific subgroups[19]. Various risk adjustment systems have been created or updated and are used in daily practice.

In the use of general outcome prediction models, several limitations should be considered: (1) Most systems produce a single estimate, known as the standardized mortality ratio (SMR). A single estimate reflects that the performance of an ICU is steady over the whole spectrum of the severity of illness[23]. In other words, an ICU with a "good" performance (low SMR) is believed to be homogeneously good for both low-risk and high-risk patients; in the same way, an ICU with a "bad" performance (high SMR) is assumed to be uniformly bad. However, since performance can vary not only between ICUs but also within the same unit across patients and doctors, this assumption is likely not true[19]. Several studies have provided conclusive documentation that the clinical performance of ICUs may vary over the array of severity of illness[2,19,24-27]; (2) It is unknown whether variations in SMR reflect quality of care or case mix differences. Debate continues whether higher than predicted mortality (high SMR) is a warning about the quality of care or rather reflects a difference of case mix between hospitals[20,28]. In the past, GOPMs have been revised or even updated to newer versions to predict expected death more accurately. However, many years elapsed before a new GOPM version was used. Although the newer third and fourth versions of the APACHE prognostic model were developed many years ago[29-31], the APACHE Ⅱ score is still one of the most widely used[9,20,32]; and (3) There is no consensus as to which GOPM must be used for which type of ICU (general mixed unit, specialized unit, or even in different sub-populations). For critical care physicians, there are three overall GOPMs for predicting overall mortality used for performance evaluations: the APACHE model[29-31,33], the MPM system[34-36] and the SAPS model[26,27,37-39]. These scoring systems differ in the choice and relative weight given to patient characteristics and physiological parameters[18,22]. Quality of care performance evaluation should be done with the same and ideally most reliable outcome prediction model for each intensive care unit. Because there is no consensus as to which GOPM should be used, they seem to be used randomly. Within the Netherlands, since 2008, all 61 participating ICUs in the NICE registry started using the APACHE Ⅳ prognostic model[18].

THE QUALITY OF INTENSIVE CARE PERFORMANCE

Until today, one of the most used ICU performance measurements is the SMR[20]. The SMR was developed in a period when the evaluation of quality of care was done exclusively through primary patient outcome (short-term

mortality). Some authors evaluated the use of SMR as an indicator of ICU quality of care and debated its specific relevance[21,40,41]. The SMR value gives insight into the observed mortality compared with the associated predicted mortality but it does not give insight into the health status of these patients.

As critical care outcomes research becomes more established, entity mortality is now only one of many endpoints that is relevant and mortality is a limited outcome evaluation method when assessing critical care performance. The health-related quality of life (HrQoL), described as the level to which a patient's health status affects the subjective appraisal of his or her contentment with life, seems to be a better indicator, especially from the patient-centered view[42]. ICU and hospital survival will always have an important role in the evaluation of performance at the moment different units or hospitals are being benchmarked. Consequently, in the last decade, the QoL has gained great interest when both physicians and patients' relatives mention patient outcome. Therefore, QoL clearly challenges survival whenever we address secondary (long-term) patient outcome.

Difficulties are being foreseen when using health status as a performance benchmark[43] because of the great diversity in intrinsic risk that patients carry in different ICUs (*i.e.*, specialized units, general mixed units)[20]. How should we use health status as performance benchmark? Should we cross-section the mean health status of a given cohort against the general population norm or must we compare individual outcome with individual pre-admission values? The latter will invariably provide more patient oriented and thus clinically relevant outcome values but also result in an administrative burden. A third possibility is to compare such an individual QoL value with a predicted individual health status.

The capability of calculating a patient's QoL after ICU admission could be useful in many ways. Firstly, it could help patients and their relatives to make decisions. Secondly, it could help families to prepare themselves to care for the patient after hospital discharge. Thirdly, it could help critical care physicians to give useful information, avoid unrealistic expectations and possibly help in making treatment decisions. Fourthly, it could help society to realize in which ICUs patients have a good prospect of recovery and give health policy makers and insurance companies insight into the needs of ICUs[42-44].

A completely different benefit using HrQoL as a performance benchmark could be the possibility of follow-up evaluation of patients' health status after ICU or hospital discharge. Post-ICU patients are known to express a reduced HrQoL compared to the general population. It is still not clear to what extent and how long this reduced HrQoL persists, although this effect may be long-lasting[45]. Therefore, a continuous survey as part of regular after care for each individual patient would be the ideal way to investigate this, providing the possibility of better managing patients in which HrQoL does not increase as expected.

READMISSION TO THE ICU: CAN WE PREDICT PATIENTS AT RISK FOR READMISSION?

The Quality Indicators Committee of the Society of Critical Care Medicine recommended that readmission within 48 h is a major performance indicator of the quality of intensive care medicine[46,47]. Readmitted patients are most often the sickest in the ICU; therefore, it is an unexpected and unfavorable event for the patient and is associated with a more severe outcome[48-57]. Moreover, a strategy to reduce premature discharges in patients at high risk of in-hospital death could result in a reduction of post-ICU mortality (Daly *et al*[58]: 39% reduction in mortality)[48,57,58]. In times of great pressure on ICU capacity, should we not be more careful in deciding which patient may be discharged and who has a greater risk of readmission? Ideally, such decisions are made on sound criteria rather than subjective parameters. In the last 10 years, several authors have proven that it is difficult to analyze and predict readmission risk for ICU patients in general[49-52]. Various authors concluded that patients readmitted to the ICU had a higher severity of illness score at the time of initial ICU discharge compared to single ICU admission patients[47,50,51,59]. Ideally perhaps, severity of illness is scored on a daily basis and discharge is initiated from these values. Unfortunately, these severity of illness scores have not been validated after the first 24 h of ICU admission. The Sequential (Sepsis-related) Organ Failure Assessment score (SOFA score) is used to track a patient's status during the admission to the ICU (also validated to be used after 24 h). The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure[60-63]. This particular score has been validated to predict ICU mortality[64]. Nevertheless, the possible association with readmission has not been evaluated as yet. Currently, there are hardly any systematic studies of how daily severity of illness score changes from admission to initial discharge predict ICU readmission[32,52]. Besides the severity of illness score, there is also an association between nursing workload and post-ICU mortality[65,66]. The Therapeutic Intervention Scoring System (TISS) has been widely applied to assess workload and resource allocation in intensive care, measuring treatment intensity[67-69]. Consequently, attempts have been made to use TISS scores to categorize the level of care that patients require and even to evaluate the care required after ICU discharge[1,68]. Several authors have shown an association of the TISS value of the last ICU day with post-ICU mortality[65,66,69,70] and therefore indirectly the association with ICU readmission. Smith *et al*[66] concluded in their research that the mean TISS scores in patients readmitted to the ICU were significantly higher than in patients who did not require readmission[65,66].

For a couple of years, Spanish physicians have shown great interest in this topic and developed the Sabadell score system, a modification of the McCabe score[71-73].

They have validated the relevance of the Sabadell score as a method for classifying patient's ward survival at discharge from the ICU[74] and even found an association of the Sabadell score with ICU readmission. Unfortunately, the lack of reliable predictors of ICU readmission prevents the clinical efficacy of this variable. However, this information may improve the ability to predict the readiness for discharge for individual patients and improve the efficiency of intensive care units[47]. Would critical care physicians have more information about patients' disease status when they use a combination of several systems (TISS, severity of illness score and Sabadell score) as a prediction measurement for ICU discharge readiness? This value could also give an indication of whether the patient could be discharged to the normal ward or if he should first be admitted to a step-down unit (high dependency unit).

Hospital death rates would be particularly useful if patients and physicians could use the statistics for a given diagnosis to select a hospital that offers the best prospect of survival. If the data are only partially corrected for differences in the health status of patients they must be used with caution[23]. Variations in case mix, ICU demographics, clinical and non-clinical factors not addressed by the present severity of illness scores must be quantified to improve the accuracy of future prediction models. If the variation between ICUs is important, it will impair the stability of the equations used to calculate predicted mortality and preclude the use of indirect standardization in the evaluation of differences between ICUs. These GOPMs consider the relationship between performance and severity of illness as constant although performance can vary within ICUs according to the level of severity of illness in patients. Hypothetically, performance should be evaluated through the combination of survival (SMR) and the health status (QoL) at the time of discharge. As yet, this combination of both outcome measurements has not been used in a single benchmark value. Therefore, future research should focus on predicting quality of life together with an accuracy study of the TISS, severity of illness and the Sabadell scores to identify and weigh the specific variables for readmission. The moment when outcome research can predict the short-term (ICU discharge) QoL of a critically ill patient during the first 24 h of ICU admission will give physicians and health care policy makers an up-to-date and reliable evaluation of quality of care in the ICU for the future.

ACKNOWLEDGMENTS

The authors declared that they have no competing interests. Each author certifies that he has participated sufficiently in the intellectual content, the analysis of data if applicable and the writing of this work to take public responsibility for it. Each has reviewed the final version of this work, believes it represents valid work and approves it for publication. We herewith state that all authors provided an equal contribution to this study and act in concordance to the "uniform requirements".

REFERENCES

1 **Mälstam J**, Lind L. Therapeutic intervention scoring system (TISS)--a method for measuring workload and calculating costs in the ICU. *Acta Anaesthesiol Scand* 1992; **36**: 758-763 [PMID: 1466209]
2 **Metnitz PG**. From risk assessment to risk management. *Curr Opin Crit Care* 2010; **16**: 475-476 [PMID: 20827074 DOI: 10.1097/MCC.0b013e32833e81ed]
3 **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]
4 **Pittoni GM**, Scatto A. Economics and outcome in the intensive care unit. *Curr Opin Anaesthesiol* 2009; **22**: 232-236 [PMID: 19390250 DOI: 10.1097/ACO.0b013e328323f9a8]
5 **Moerer O**, Plock E, Mgbor U, Schmid A, Schneider H, Wischnewsky MB, Burchardi H. A German national prevalence study on the cost of intensive care: an evaluation from 51 intensive care units. *Crit Care* 2007; **11**: R69 [PMID: 17594475]
6 **Chalfin DB**. Cost-effectiveness analysis in health care. *Hosp Cost Manag Account* 1995; **7**: 1-8 [PMID: 10143321]
7 **Zilberberg MD**, Luippold RS, Sulsky S, Shorr AF. Prolonged acute mechanical ventilation, hospital resource utilization, and mortality in the United States. *Crit Care Med* 2008; **36**: 724-730 [PMID: 18209667 DOI: 10.1097/CCM.0B013E31816536F7]
8 **Halpern NA**, Bettes L, Greenstein R. Federal and nationwide intensive care units and healthcare costs: 1986-1992. *Crit Care Med* 1994; **22**: 2001-2007 [PMID: 7988140]
9 **Fakhry SM**, Martin B, Al Harakeh H, Norcross ED, Ferguson PL. Proportional costs in trauma and acute care surgery patients: dominant role of intensive care unit costs. *J Am Coll Surg* 2013; **216**: 607-614; discussion 614-616 [PMID: 23415554 DOI: 10.1016/j.jamcollsurg.2012.12.031]
10 **Halpern NA**, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. *Crit Care Med* 2004; **32**: 1254-1259 [PMID: 15187502]
11 **Halpern NA**, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med* 2010; **38**: 65-71 [PMID: 19730257 DOI: 10.1097/CCM.0b013e3181b090d0]
12 **Halpern NA**. Can the costs of critical care be controlled? *Curr Opin Crit Care* 2009; **15**: 591-596 [PMID: 19823083 DOI: 10.1097/MCC.0b013e328332f54f]
13 **Cohen NH**. Critical care medicine in the United States: what we know, what we do not, and where we go from here. *Crit Care Med* 2010; **38**: 304-306 [PMID: 20023473 DOI: 10.1097/CCM.0b013e3181b4a2b6]
14 **Kahn JM**, Angus DC. Reducing the cost of critical care: new challenges, new solutions. *Am J Respir Crit Care Med* 2006; **174**: 1167-1168 [PMID: 17110650]
15 **Vincent JL**, Opal SM, Marshall JC. Ten reasons why we should NOT use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med* 2010; **38**: 283-287 [PMID: 19730252 DOI: 10.1097/CCM.0b013e3181b785a2]
16 **OECD library**. Organisation for Economics Co-operation and Development: Health at a Glance: OECD indicators. 2005 [DOI: 10.1787/9789264012639-en]
17 **Wunsch H**, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA, de Keizer NF, Kersten A, Linde-Zwirble WT, Sandiumenge A, Rowan KM. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008; **36**: 2787-2793 [PMID: 18766102 DOI: 10.1097/CCM.0b013e318186aec8]
18 Available from: URL: http: //www.NVIC.nl
19 **Moreno RP**, Hochrieser H, Metnitz B, Bauer P, Metnitz PG. Characterizing the risk profiles of intensive care units. *In-*

tensive Care Med 2010; **36**: 1207-1212 [PMID: 20306015 DOI: 10.1007/s00134-010-1852-2]
20 **Timmers TK**, Joore HC, Leenen LP. Changes after transformation from a specialized surgical unit to a general mixed intensive care unit. *Crit Care Nurs Q* 2014; **37**: 115-124 [PMID: 24309465 DOI: 10.1097/CNQ.0000000000000010]
21 **Teres D**, Lemeshow S. Why severity models should be used with caution. *Crit Care Clin* 1994; **10**: 93-110; discussion 111-115 [PMID: 8118735]
22 **De Lange DW**, Dusseljee J, Brinkman S, van Berkel G, van Maanen R, Bosman RJ, Joore H, de Keizer NF, van der Voort PHJ, de Waal R, Wesselink RMJ, de Jonge E. Severity of illness and outcome in ICU patients in the Netherlands: results from the NICE registry 2006-2007. *Nether J Crit Care* 2009; **13**: 16-22
23 **Moreno R**, Apolone G. Impact of different customization strategies in the performance of a general severity score. *Crit Care Med* 1997; **25**: 2001-2008 [PMID: 9403750]
24 **Moreno RP**, Bauer P, Metnitz PG. Characterizing performance profiles of ICUs. *Curr Opin Crit Care* 2010; **16**: 477-481 [PMID: 20613499 DOI: 10.1097/MCC.0b013e32833cc925]
25 **Civetta JM**. Scoring systems: do we need a different approach? *Crit Care Med* 1991; **19**: 1460-1461 [PMID: 1959362]
26 **Metnitz PG**, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med* 2005; **31**: 1336-1344 [PMID: 16132893]
27 **Moreno RP**, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 2005; **31**: 1345-1355 [PMID: 16132892]
28 **Green J**, Passman LJ, Wintfeld N. Analyzing hospital mortality. The consequences of diversity in patient mix. *JAMA* 1991; **265**: 1849-1853 [PMID: 1900894]
29 **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]
30 **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]
31 **Zimmerman JE**, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; **34**: 1297-1310 [PMID: 16540951]
32 **Cohen NH**. The real reasons not to rely on severity scores. *Crit Care Med* 2010; **38**: 334-335 [PMID: 20023491 DOI: 10.1097/CCM.0b013e3181b9d3e4]
33 **Knaus WA**, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; **9**: 591-597 [PMID: 7261642]
34 **Lemeshow S**, Teres D, Avrunin JS, Gage RW. Refining intensive care unit outcome prediction by using changing probabilities of mortality. *Crit Care Med* 1988; **16**: 470-477 [PMID: 3359785]
35 **Lemeshow S**, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA* 1993; **270**: 2478-2486 [PMID: 8230626]
36 **Higgins TL**, Teres D, Copes WS, Nathanson BH, Stark M, Kramer AA. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007; **35**: 827-835 [PMID: 17255863]
37 **Le Gall JR**, Loirat P, Alperovitch A, Glaser P, Granthil C, Mathieu D, Mercier P, Thomas R, Villers D. A simplified acute physiology score for ICU patients. *Crit Care Med* 1984; **12**: 975-977 [PMID: 6499483]
38 **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]
39 **Le Gall JR**, Neumann A, Hemery F, Bleriot JP, Fulgencio JP, Garrigues B, Gouzes C, Lepage E, Moine P, Villers D. Mortality prediction using SAPS II: an update for French intensive care units. *Crit Care* 2005; **9**: R645-R652 [PMID: 16280063]
40 **Sherck JP**, Shatney CH. ICU scoring systems do not allow prediction of patient outcomes or comparison of ICU performance. *Crit Care Clin* 1996; **12**: 515-523 [PMID: 8839587]
41 **Boyd O**, Grounds M. Can standardized mortality ratio be used to compare quality of intensive care unit performance? *Crit Care Med* 1994; **22**: 1706-1709 [PMID: 7924389]
42 **Capuzzo M**, Moreno RP, Jordan B, Bauer P, Alvisi R, Metnitz PG. Predictors of early recovery of health status after intensive care. *Intensive Care Med* 2006; **32**: 1832-1838 [PMID: 16896849]
43 **Valentin A**. The importance of risk reduction in critically ill patients. *Curr Opin Crit Care* 2010; **16**: 482-486 [PMID: 20613502 DOI: 10.1097/MCC.0b013e32833cb861]
44 **Angus DC**. Caring for the critically ill patient: challenges and opportunities. *JAMA* 2007; **298**: 456-458 [PMID: 17652301]
45 **Timmers TK**, Verhofstad MH, Moons KG, van Beeck EF, Leenen LP. Long-term quality of life after surgical intensive care admission. *Arch Surg* 2011; **146**: 412-418 [PMID: 21173281 DOI: 10.1001/archsurg.2010.279]
46 **Angus DC**. Grappling with intensive care unit quality--does the readmission rate tell us anything? *Crit Care Med* 1998; **26**: 1779-1780 [PMID: 9824061]
47 **Timmers TK**, Hulstaert PF, Leenen LP. Patient outcomes can be associated with organizational changes: a quality improvement case study. *Crit Care Nurs Q* 2014; **37**: 125-134 [PMID: 24309466 DOI: 10.1097/CNQ.0000000000000011]
48 **Metnitz PG**, Fieux F, Jordan B, Lang T, Moreno R, Le Gall JR. Critically ill patients readmitted to intensive care units--lessons to learn? *Intensive Care Med* 2003; **29**: 241-248 [PMID: 12594586]
49 **Chen LM**, Martin CM, Keenan SP, Sibbald WJ. Patients readmitted to the intensive care unit during the same hospitalization: clinical features and outcomes. *Crit Care Med* 1998; **26**: 1834-1841 [PMID: 9824076]
50 **Alban RF**, Nisim AA, Ho J, Nishi GK, Shabot MM. Readmission to surgical intensive care increases severity-adjusted patient mortality. *J Trauma* 2006; **60**: 1027-1031 [PMID: 16688065]
51 **Rosenberg AL**, Watts C. Patients readmitted to ICUs*: a systematic review of risk factors and outcomes. *Chest* 2000; **118**: 492-502 [PMID: 10936146]
52 **Rosenberg AL**, Hofer TP, Hayward RA, Strachan C, Watts CM. Who bounces back? Physiologic and other predictors of intensive care unit readmission. *Crit Care Med* 2001; **29**: 511-518 [PMID: 11373413]
53 **Nishi GK**, Suh RH, Wilson MT, Cunneen SA, Margulies DR, Shabot MM. Analysis of causes and prevention of early readmission to surgical intensive care. *Am Surg* 2003; **69**: 913-917 [PMID: 14570374]
54 **Lee HF**, Lin SC, Lu CL, Chen CF, Yen M. Revised Acute Physiology and Chronic Health Evaluation score as a predictor of neurosurgery intensive care unit readmission: a case-controlled study. *J Crit Care* 2010; **25**: 294-299 [PMID: 20189751 DOI: 10.1016/j.jcrc.2009.12.007]
55 **Kaben A**, Corrêa F, Reinhart K, Settmacher U, Gummert J, Kalff R, Sakr Y. Readmission to a surgical intensive care unit: incidence, outcome and risk factors. *Crit Care* 2008; **12**: R123 [PMID: 18838006 DOI: 10.1186/cc7023]

56 **Chan KS**, Tan CK, Fang CS, Tsai CL, Hou CC, Cheng KC, Lee MC. Readmission to the intensive care unit: an indicator that reflects the potential risks of morbidity and mortality of surgical patients in the intensive care unit. *Surg Today* 2009; **39**: 295-299 [PMID: 19319635 DOI: 10.1007/s00595-008-3876-6]

57 **Afessa B**, Keegan MT, Hubmayr RD, Naessens JM, Gajic O, Long KH, Peters SG. Evaluating the performance of an institution using an intensive care unit benchmark. *Mayo Clin Proc* 2005; **80**: 174-180 [PMID: 15704771]

58 **Daly K**, Beale R, Chang RW. Reduction in mortality after inappropriate early discharge from intensive care unit: logistic regression triage model. *BMJ* 2001; **322**: 1274-1276 [PMID: 11375229]

59 **Durbin CG**, Kopel RF. A case-control study of patients readmitted to the intensive care unit. *Crit Care Med* 1993; **21**: 1547-1553 [PMID: 8403966]

60 **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]

61 **Vincent JL**, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; **26**: 1793-1800 [PMID: 9824069]

62 **Moreno R**, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, Bruining H, Willatts S. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. *Intensive Care Med* 1999; **25**: 686-696 [PMID: 10470572]

63 **de Mendonça A**, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 2000; **26**: 915-921 [PMID: 10990106]

64 **Ferreira FL**, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; **286**: 1754-1758 [PMID: 11594901]

65 **Moreno R**, Miranda DR, Matos R, Fevereiro T. Mortality after discharge from intensive care: the impact of organ system failure and nursing workload use at discharge. *Intensive Care Med* 2001; **27**: 999-1004 [PMID: 11497159]

66 **Smith L**, Orts CM, O'Neil I, Batchelor AM, Gascoigne AD, Baudouin SV. TISS and mortality after discharge from intensive care. *Intensive Care Med* 1999; **25**: 1061-1065 [PMID: 10551959]

67 **Cullen DJ**, Civetta JM, Briggs BA, Ferrara LC. Therapeutic intervention scoring system: a method for quantitative comparison of patient care. *Crit Care Med* 1974; **2**: 57-60 [PMID: 4832281]

68 **Keene AR**, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. *Crit Care Med* 1983; **11**: 1-3 [PMID: 6848305]

69 **Capuzzo M**, Moreno RP, Alvisi R. Admission and discharge of critically ill patients. *Curr Opin Crit Care* 2010; **16**: 499-504 [PMID: 20644469 DOI: 10.1097/MCC.0b013e32833cb874]

70 **Beck DH**, McQuillan P, Smith GB. Waiting for the break of dawn? The effects of discharge time, discharge TISS scores and discharge facility on hospital mortality after intensive care. *Intensive Care Med* 2002; **28**: 1287-1293 [PMID: 12209279]

71 **Fernandez R**, Baigorri F, Navarro G, Artigas A. A modified McCabe score for stratification of patients after intensive care unit discharge: the Sabadell score. *Crit Care* 2006; **10**: R179 [PMID: 17192174]

72 Sabadell Score. Available from: URL: http: //www.sabadellscore.es

73 **McCabe WR**, Jackson GG. Gram negative bacteremia: I. Etiology and ecology. *Arch Intern Med* 1962; **110**: 845-847

74 **Fernandez R**, Serrano JM, Umaran I, Abizanda R, Carrillo A, Lopez-Pueyo MJ, Rascado P, Balerdi B, Suberviola B, Hernandez G. Ward mortality after ICU discharge: a multicenter validation of the Sabadell score. *Intensive Care Med* 2010; **36**: 1196-1201 [PMID: 20221748 DOI: 10.1007/s00134-010-1825-5]

P- Reviewer: Pittet V, Wan TTH **S- Editor**: Ji FF
L- Editor: Roemmele A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v3.i4.80

World J Crit Care Med 2014 November 4; 3(4): 80-94
ISSN 2220-3141 (online)

REVIEW

Focus on peripherally inserted central catheters in critically ill patients

Paolo Cotogni, Mauro Pittiruti

Paolo Cotogni, Anesthesiology and Intensive Care, Department of Medicine, S. Giovanni Battista Hospital, University of Turin, 10123 Turin, Italy
Mauro Pittiruti, Department of Surgery, Catholic University Hospital, 00168 Rome, Italy
Author contributions: Cotogni P and Pittiruti M developed the research question and review design; Cotogni P drafted and finalized the manuscript; all authors revised and approved the final version.
Correspondence to: Paolo Cotogni, MD, 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: +39-011-5171634 Fax: +39-011-6334324
Received: June 16, 2014 Revised: September 25, 2014
Accepted: October 14, 2014
Published online: November 4, 2014

Abstract

Venous access devices are of pivotal importance for an increasing number of critically ill patients in a variety of disease states and in a variety of clinical settings (emergency, intensive care, surgery) and for different purposes (fluids or drugs infusions, parenteral nutrition, antibiotic therapy, hemodynamic monitoring, procedures of dialysis/apheresis). However, healthcare professionals are commonly worried about the possible consequences that may result using a central venous access device (CVAD) (mainly, bloodstream infections and thrombosis), both peripherally inserted central catheters (PICCs) and centrally inserted central catheters (CICCs). This review aims to discuss indications, insertion techniques, and care of PICCs in critically ill patients. PICCs have many advantages over standard CICCs. First of all, their insertion is easy and safe -due to their placement into peripheral veins of the arm- and the advantage of a central location of catheter tip suitable for all osmolarity and pH solutions. Using the ultrasound-guidance for the PICC insertion, the risk of hemothorax and pneumothorax can be avoided, as well as the possibility of primary malposition is very low. PICC placement is also appropriate to avoid post-procedural hemorrhage in patients with an abnormal coagulative state who need a CVAD. Some limits previously ascribed to PICCs (*i.e.*, low flow rates, difficult central venous pressure monitoring, lack of safety for radio-diagnostic procedures, single-lumen) have delayed their start up in the intensive care units as common practice. Though, the recent development of power-injectable PICCs overcomes these technical limitations and PICCs have started to spread in critical care settings. Two important take-home messages may be drawn from this review. First, the incidence of complications varies depending on venous accesses and healthcare professionals should be aware of the different clinical performance as well as of the different risks associated with each type of CVAD (CICCs or PICCs). Second, an inappropriate CVAD choice and, particularly, an inadequate insertion technique are relevant-and often not recognized-potential risk factors for complications in critically ill patients. We strongly believe that all healthcare professionals involved in the choice, insertion or management of CVADs in critically ill patients should know all potential risk factors of complications. This knowledge may minimize complications and guarantee longevity to the CVAD optimizing the risk/benefit ratio of CVAD insertion and use. Proper management of CVADs in critical care saves lines and lives. Much evidence from the medical literature and from the clinical practice supports our belief that, compared to CICCs, the so-called power-injectable peripherally inserted central catheters are a good alternative choice in critical care.

Key words: Central venous catheters; Venous access devices; Ultrasound guidance; Guidelines; Peripherally inserted central catheters; Blood stream infections; Intensive care unit patients; Critical care medicine; Pediatrics

Core tip: The placement and care of central venous

access devices (CVADs) are key elements of management for either adult or pediatric critically ill patients. Healthcare professionals are commonly worried about complications related to the employ of a CVAD due to increasing costs, hospitalization, and mortality. The rate of catheter-related complications is often related to an out-of-date decision-making of healthcare professionals who manage the CVAD. This review may be useful for guiding healthcare professionals to choose the right device, placement technique, and care of CVADs with the aim of reducing the possibility of complications in critically ill patients.

Cotogni P, Pittiruti M. Focus on peripherally inserted central catheters in critically ill patients. *World J Crit Care Med* 2014; 3(4): 80-94 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i4/80.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i4.80

INTRODUCTION

Since the 1970's, the most appropriate way for safe and prolonged administration of drugs and fluids in hospitalized patients are the central venous access devices (CVADs)-typically in the perioperative period and/or in the intensive care unit (ICU). In-hospital subjects requiring intravenous (*iv*) therapies for an extended time should be routinely assessed for an adequate and stable CVAD, considering the emerging evidence that its early use led to higher patient preference and adherence, reduced discontinuations in infusion associated to failure of CVAD, less catheter-related adverse events (*i.e.*, dislocation and infiltration), conservation of "venous bed" of arms and forearms, reduced consuming-time for nurses to repeatedly insert a venous device, and decreased infusion therapy costs, compared with the use of peripheral short-term cannulas[1]. In particular, a CVAD is mandatory for a number of infusions, such as vesicant/irritant drugs, solutions with pH lower than 5 and higher than 9 (*e.g.*, vancomycin, levofloxacin, dopamine) or hyperosmolar parenteral nutrition (*i.e.*, whose osmolarity exceeds 800-900 mOsm/L).

The insertion and care of a CVAD are integral elements of management for adult and pediatric hospitalized patients. Based on data coming from United States, almost five million of CVADs are annually placed[2]. Therefore, no data are available about the exact number of CVAD placement in critically ill patients, but it is realistic to presume that the proportion is relevant, as it is widely accepted that critically ill patients require a central VAD for the optimal management of their disease.

However, healthcare professionals (HPs) are commonly worried about potential risks related to the presence of a CVAD, in particular catheter-related bloodstream infections (CRBSIs), because of morbidity, mortality, and costs[3]. The most expensive and dangerous healthcare-associated infection is CRBSI. In the United States it was reported an incidence of approximately 80000 CRBSI every year in hospitalized patients and almost 50% of cases occurred in ICU. The number of subjects dying each year for CVAD-related sepsis is between 14000-28000. Each central line sepsis costs $29000 and increases hospital length of stay by seven days[4].

The incidence of CRBSI is often related to an inadequate implementation of proper aseptic policies and insufficient training of the physicians and nurses who insert and maintain the CVAD. Moreover, emerging data describe other important but often overlooked risk factors for catheter-related complications (CRCs): the choice of a CVAD that is inappropriate for that clinical situation; the cannulation of a vein too small for the CVAD needed; the insertion of CVAD without ultrasound guidance, for instance by "blind" infraclavicular venipuncture of the subclavian vein (SV); inappropriate exit site of the CVAD; routine utilize of sutures to secure the CVAD; failure to recognize the importance of a right placement of the CVAD tip[5,6], *etc.*

In recent years, there have been a widespread dissemination of several technological innovations which improve the security of CVADs [ultrasound (US)-guided vein puncture, innovative materials, peripherally placement of CVAD, sutureless materials to secure CVADs], as well as novel actions apt to reduce the incidence of CRCs [well-defined and accepted procedures (the so-called "bundles"), meticulous adherence to protocols for hand-washing, training programs for HPs, utilize of accurate antisepsis of the skin, and so on][7,8].

The present review aims to discuss indications and management of CVADs in adult and pediatric critically ill patients; in particular, this review will focus on peripherally inserted central catheters (PICCs). We hope that this review may be clinically useful for guiding all HPs to proper choice, technique of insertion, and care of CVADs so to decrease the incidence of catheter-related complications and draw out the duration of the CVAD in critically ill patients.

CHOICE OF THE VAD

The term central venous catheter has been avoided, since it may be ambiguous (PICCs are central venous catheters, too) and replaced by centrally inserted central catheters (CICCs), as opposed to PICCs, or by "CVAD" (term which includes both PICCs and CICCs).

The list of VADs potentially usable in acutely ill patients includes midline catheters, CICCs, and PICCs.

Midline catheters and PICCs are commonly regarded as "medium term VADs", while non-tunneled CICCs are regarded as "short term VADs"[8]. This review will not discuss "long-term CVADs" (tunneled and cuffed central devices or totally implantable catheters, *i.e.*, ports), since they have no indication in the critical care setting. Pre-existing long term VADs in critically ill patients should not be used in ICU and even removed if suspected to be source of infection.

Midline are 20-25 cm long non-tunneled venous de-

vices (polyurethane- or silicone-made), whose diameter is generally 3-5 Fr. Midline catheters are placed into antecubital or cephalic veins located in the region of the arm in front of the elbow (the so-called antecubital area)[9], employing the "blind" percutaneous procedure, or preferably by US-guided venipuncture of arm deep veins[10]. Therefore, the tip position of these VADs is not "central", *i.e.*, is not in superior vena cava (SVC) or in right atrium (RA), but in axillary vein (AV) or in SV. A grade B recommendation of the guidelines states that the Midline has to be considered an alternative choice whenever a parenteral therapy trough a peripheral vein is planned for a period longer than six days[7]. Thus, a use of midline catheters should be preferred because short vein cannulas usually lead to an important rate of infiltration and dislocation and ask for a strict surveillance. However, midline catheters have their major limitation in the risk of peripheral venous thrombosis (the so-called "thrombophlebitis")[11]. Moreover, critically ill patients usually require a CVAD for infusions of drugs associated with endothelial damage or hyperosmolar parenteral nutrition or monitoring.

Centrally inserted central catheters are generally 20 to 30 cm long non-tunneled venous devices (polyurethane-made) placed in a deep central vein [internal jugular vein (IJV), SV, AV, or innominate vein] as well as in the femoral veins (FVs). These VADs are intended for continuous use; they are commonly inserted in ICU and non-ICU patients and used for a short period of time (days or weeks)[12]. CICCs may have either a single lumen or from 2 to 5 lumens.

Peripherally inserted central catheters are 50 to 60 cm long non-tunneled central catheters (silicone- or Ⅱ-Ⅲ generation polyurethane-made). PICCs are placed *via* a peripheral vein (*i.e.*, basilic vein, brachial vein, or -less frequently- cephalic vein) of the arm. They can be used for continuous or intermittent *iv* fluid and drug administrations, either in inpatients or outpatients (in ambulatory or day-hospital), at home for home parenteral nutrition, or in hospice for palliative care for prolonged periods of time[12,13]. Generally, PICCs are inserted by doctors or nowadays more frequently by registered nurses at the bedside. Currently, they are preferably inserted in a deep vein of the upper midarm by US-guidance. One, two or three lumens PICCs are presently available.

Indications for PICCs

Nowadays, PICCs are being increasingly used in critical care settings[14] because of their benefits over CICCs. Firstly, their insertion is easy and safe, as it implies puncture and cannulation of a peripheral vein of the arm. Using the US-guidance for the PICC insertion, the risk of hemothorax and pneumothorax can be avoided, as well as the possibility of primary malposition is very low[7,15]. Also, PICC placement is appropriate to avoid post-procedural hemorrhage in patients with coagulative disorders who need a CVAD[7,8].

At present, PICCs are highly recommended in the following clinical conditions: major anatomic abnormalities of the chest and neck that may lead to difficulties in the placement and dressing of CICCs, tracheostomy and decreased platelet count or coagulation abnormalities[7]. Some authors suggests that PICCs are also highly recommended in critically ill patients with severe cardiopulmonary problems or severe malnutrition and obesity[15].

The commonly accepted contraindications to PICC insertion are: (1) small diameter of arm veins (basilic or brachial) (*i.e.*, < 3-4 mm); (2) femoral access necessary because of a mediastinal syndrome; and (3) particular conditions of the arms (*e.g.*, paresis, local infection of the skin, presence of devices due to orthopedic procedures with a block of the arm, local severe burns, earlier removal of lymphatic nodes of the axilla). PICCs are also contra-indicated in case of severe renal impairment associated with a potential dialysis indication due to critical need to preserve the deep veins of the arms for the placement of an arteriovenous fistula. Further, is mandatory a CICC in case of need of multiple lumens (*i.e.*, > 3 lumens). Finally, all CVADs placed as emergency procedure should preferably be CICCs[15].

INSERTION OF THE VAD

Site of insertion

Generally speaking, the choice of site of insertion of the most appropriate CVAD should be "patient-oriented"; thus, related to his/her previous VAD placements, status of "vascular bed", anatomy of deep veins, history of coagulation disorders, underlying disease, and, mainly, duration and characteristics of all planned therapies. The choice of the vein for the CVAD is influenced by aspects such as the venipuncture method, the likelihood of CRCs (*i.e.*, infectious, thrombotic, and mechanical) and the practicability of proper management of the exit site of the CVAD[7].

Commonly, there are two methods for percutaneous insertion of the CICCs into central veins: (1) by using the anatomic landmarks (*i.e.*, the "blind" technique); and (2) by the US-guided venipuncture. Using the anatomic landmarks, the SV (through an infraclavicular or supraclavicular *via*), the IJV (with different approaches: *e.g.*, low lateral, high anterior or posterior, and axial among the 2 heads of sternoclavicular muscle), or the FV are the veins generally chosen. Comparison between technical success and outcome of CVADs *via* "blind" cannulation of IJV and SV demonstrated a decrease in adverse events associated with the insertion for an jugular approach[16]. A retrospective survey of more than 5400 CVAD insertions showed that the low lateral approach to the IJV (the technique of Jernigan) is the easiest and safest method for "blind" cannulation because of the lowest rate of insertion-related adverse events[17].

Adopting US-guided venipuncture, CICCs are inserted by supraclavicular approach to the innominate vein, the IJV, or the SV; by infraclavicular approach to the AV/SV; and into the FV. This latter approach is relatively contraindicated unless no other venous access can be

obtained because the insertion of a non-tunneled VAD in the FV is related to a higher rate of complications (*e.g.*, thrombosis and contamination at the exit site at the groin)[18]. In the case of VAD placed in the FV, its exit site has to be positioned properly distant from the groin to reduce the danger of contamination.

A review published in 2003[19] has suggested that choice of the SV seems to reduce the incidence of infections. Nevertheless, although this assertion was attested by a randomized controlled trial (RCT) bringing into comparison the incidence of infectious complications linked to the choice of SV or FV[20], it is not available a RCT that compares the infectious occurrence related to the jugular or subclavian approach. In 2007, a comprehensive analysis by Cochrane Collaboration did not find satisfactory RCTs regarding SV *vs* IJV and concluded that, to define the best method between the subclavian or the jugular approach, it would be necessary to collect more data[21]. A prospective analysis in about a thousand oncologic patients[22] showed that all CRCs (*i.e.*, immediate complications, catheter malposition, venous thrombosis, and long-term morbidity) were significantly more recurring in the SV than in the IJV. A recent review investigating the risk of CRBSIs associated with VADs placed in the FV evaluated this approach with SV and IJV insertion and showed equivalence in the incidence of VAD-related infections between the three sites[23].

Although several studies compared complication rate associated to the SV, IJV, and FV placements in ICU, data are not conclusive. Lorente *et al*[24] reported in a case series of a thousand critically ill patients, the IJV and the FV were related to an increased rate of infectious complications at the catheter exit site; however, there was equivalence in reference to CVAD-related bloodstream infections[24]. A non-RCT evaluating the SV, IJV, and FV exit sites in ICU demonstrated that overall incidence of both colonization and infection of the VAD is not relevant and similar between the three sites, provided that optimal VAD management is adopted[25].

All these previous findings are biased by the fact that often these studies were carried out in the "pre-ultrasound" era, when the only choice was between IJV (mostly associated with an exit site at mid-neck, particularly unstable and at high risk for contamination) and SV (mostly associated with an exit site in the infraclavicular area): also, the actual diameter of the vein was not known, so that the real risk of thrombosis could not be assessed.

Since most guidelines currently recommend the use of ultrasound guided venipuncture[26], the choice is today between the catheter site in supraclavicular area (puncture of SV, IJV, or innominate vein by US guidance) *vs* the catheter site in infraclavicular area (insertion into the AV by US guidance). At mid-neck the catheter exit site should be avoided: if it is in the neck upper part, either a higher possibility of colonization or CRBSI, related to the mobilization of the neck, or a greater difficulty with the dressing of the exit site are to be expected[27]. Thus, it is preferable to choose an exit site that facilitates the changes of exit site-dressing, like the zone immediately above the clavicle (the supraclavicular technique to innominate vein or SV; the Jernigan's method to IJV) or the infraclavicular area (AV).

On the left side, the insertion of CVADs can frequently lead to an increased possibility of primary malposition and thrombosis; for this reason, the insertion on the right side is to be preferred. Though, some specific clinical (*e.g.*, chest or pulmonary diseases, skin abnormalities) or anatomic conditions (poor US vein view) may recommend the use of one or the contralateral side.

Current guidelines on prevention of catheter-related thrombosis[28,29] recommend the use of ultrasound, the appropriate match of vein diameter and catheter diameter, the appropriate "central" position of the tip, and the diameter of CVADs as little as possible[8].

US guidance

In a recent paper, an international panel of experts defined the US-guided insertion of a vascular access[26]. Summarizing, this definition states that US guidance is useful for verifying the location of an appropriate vascular access before the needle introduction, as well as for real-time US scanning to direct the tip of the needle all the way through the venipuncture (Figures 1 and 2).

There are different evident clinical advantages with US vascular imaging; first, it shows a healthy vein before VAD insertion[30,31]. Second, the US-guided skin puncture increases the chances of the insertion of the needle into the vein during the initial attempt with the benefit of minimizing the possibility of adverse events[32,33]. Finally, US imaging can confirm correct position of the VAD tip[34]. The advantages of US-guidance are demonstrated for both CICCs or PICCs and long-term CVADs (tunneled or totally implanted)[35].

Since the late 1990's, many RCTs and meta-analyses have demonstrated the benefits of the US-guided insertion of CVADs[36]. Several meta-analyses on this subject confirmed that the use of US guidance is characterized by many advantages in comparison to the "blind" technique: a reduced incidence of insertion failure, insertion-related adverse events (*e.g.*, pneumothorax and accidental arterial puncture), and thus an increased incidence of successful insertion at the primary venipuncture, along with fewer CRCs (thrombotic and infectious complications) and of costs[37-39]. Therefore, since the beginning of new millennium, evidence-based guidelines produced by several scientific societies and healthcare organizations[7,29,40-49] have strongly recommended the use of US guidance for increasing efficacy and safety of CVAD insertion in both adults and children[7]. Prospective, nonrandomized investigations have demonstrated that the rate of catheter-related thrombosis is reduced avoiding the injury of the wall of the vein during the placement, as obtained *via* US-guided insertion[7].

In summary, evidence and broad consensus suggest that US guidance before skin puncture and through the

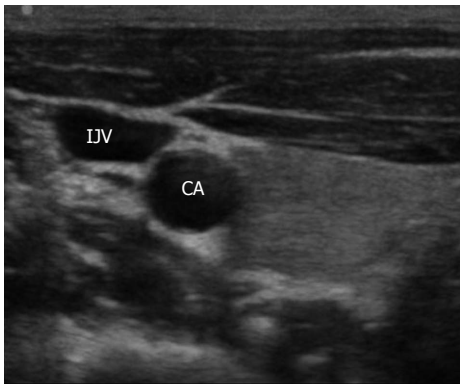


Figure 1 Ultrasound visualization of the internal jugular vein and the carotid artery on the right side of the neck. IJV: Internal jugular vein; CA: Carotid artery.

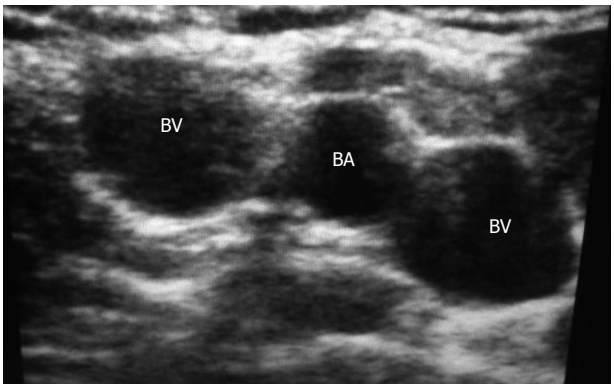


Figure 2 Ultrasound visualization of vessels of right upper arm: the brachial artery is the middle of two brachial veins. BA: Brachial artery; BV: Brachial veins.

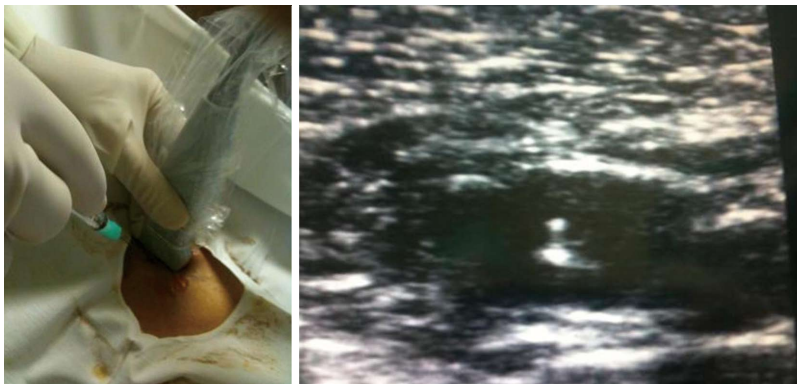


Figure 3 Ultrasound-guided venipuncture of the axillary vein.

vein cannulation is related to reductions of insertion-related adverse events and costs, as well as a more rapid placement of the CVAD[7,30,32,36-38,45,50-53]. Thus, nowadays it may be judged unethical to deny the employ of the US guidance[7,54].

It is possible that the ideal venous approach for CVAD in the near future will be the US-guided puncture of the axillary vein, which combines the advantages to have an "ideal" catheter exit site (*i.e.*, infraclavicular area) and an "ideal" complication-free insertion (Figure 3).

Single vs multiple-lumen

The Center for Disease Control and Prevention (CDC) guidelines[44] and a RCT[55] stated that comparing multiple lumens to single lumen CVAD, the first one showed increased incidence of infections. The issue has been also evaluated by a meta-analysis and a review that investigated both the rate of colonization and CRBSI in multi-lumen and single-lumen CVADs. The meta-analysis demonstrated that multi-lumens CVADs are not an independent variable for higher colonization and CRBSI[56]. The review showed that findings from five randomized studies documented that, for each twenty single lumen CVADs placed in, one CRBSI that would have taken place if had multiple lumen CVADs been inserted, will instead be prevented[57].

When a multi-lumen CVAD is inserted, it is recommended to use one lumen just for parenteral nutrition. In fact, if nutrient emulsions, pharmacological agents, or any parenteral infusion of dissimilar pH get in contact, the possibility of precipitates and, therefore, the risk of infectious complications, increases. Moreover, lipid containing parenteral nutrition bags should be infused through the largest lumen of the CVAD, so to reduce the risk of lumen obstruction[40]. Obviously, each lumen has to be managed with an equal careful awareness to the asepsis. Although further studies are necessary in this regard, currently single lumen CVADs are to be preferred, except if a multi-lumen CVAD is necessary for patient care[7].

Stabilization

Different devices are commonly used to secure CVADs to the skin: strips, tapes, sutures, and manufactured catheter-stabilization devices (*i.e.*, sutureless devices) (Figures 4 and 5); indeed, a fully consideration to sutureless devices should be nowadays given[7]. In particular, sutures would be better to be avoided because of the increasing of the incidence of vein phlebitis and thrombosis (in case of PICCs), CRBSIs (in case of CICCs), and exit site infection and catheter dislocation (in every CVADs)[58].

Tip position

A crucial relevance has the position of the tip that must be always checked after every placement of a CVAD.

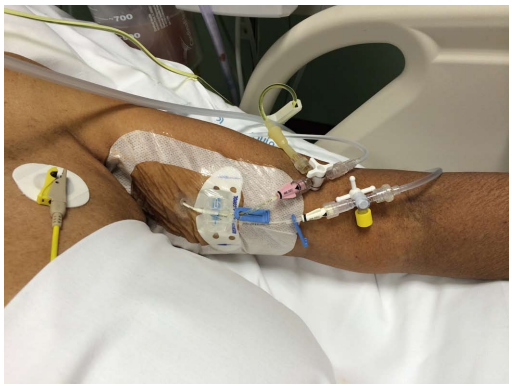


Figure 4 Stabilization with a sutureless device of a peripherally inserted central catheter.

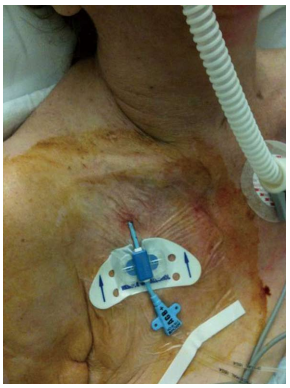


Figure 5 Stabilization with a sutureless device of a centrally inserted central catheter.

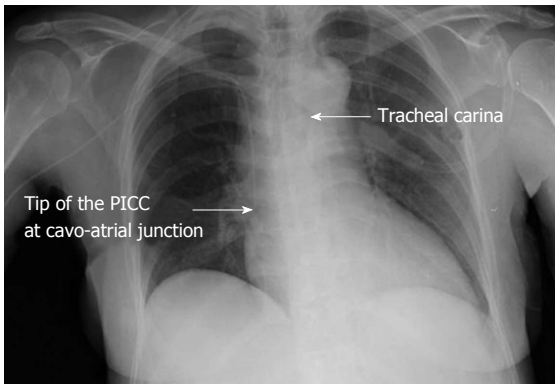


Figure 6 Post-procedural chest X-ray. The left arrow shows the tip position of the peripherally inserted central catheter (PICC) that is at cavo-atrial junction (between the superior vena cava and the right atrium). The right arrow shows the tracheal carina.

However, there is no widespread agreement between the experts regarding the correct position for the tip of a CVAD[59]. Most American recommendations (Association for Vascular Access, Food and Drug Administration)[60-62] suggest that the tip has to be in the inferior 1/3 of superior vena cava, while European guidelines[7,46] often consider the position of the tip in the RA (specifically, in the upper area) as appropriate. A wide accepted opinion is that the optimal site is proximal to the area among SVC and RA[63] [*i.e.*, the cavo-atrial junction-(CAJ)] (Figure 6).

Evidence from several prospective studies suggests that an inappropriate tip position is one of the primary causes of CVAD thrombotic complications, as well as the principal cause of catheter failure (mainly, due to malfunction) and decreased catheter dwell time. In fact, if catheter tip is in a higher position (*i.e.*, middle third or upper third of the SVC, or in the brachiocephalic, or in the IJV, or in the SV), there is an increased risk of malfunction[64] and an increased risk of venous thrombosis if compared to a lower position into the superior cava vein or close to the CAJ[65]. If the tip is positioned "too low" (right atrium, right ventricle or inferior vena cava), there is a risk of arrhythmias, tricuspid valve dysfunction or lesions, and thrombosis[19,66,67]. Malpositions are classified as "primary" when malposition occurs during the insertion (*e.g.*, catheter tip into the ipsilateral IJV, as well as into the opposite brachiocephalic vein/SV/IJV) while as "secondary" when the catheter tip migrates spontaneously in the weeks or months following the insertion. The overall incidence of "primary" malpositions varies from 2% to 30%. Clinical experience suggests that malposition occurs more frequently when the left veins are chosen for CVAD placement.

Indeed, during insertion, some methods may significantly reduce the risk of a catheter being placed too "high" or too "low". The most commonly used "post-procedural" method is the standard chest X-ray. This method is appropriate to verify the exact position of the tip, with few false negatives (mainly due to technical problems or X-ray artifacts) and very few false positive results (*e.g.*, tip position into internal mammary veins and hemiazygos veins). However, "post-procedural" diagnosis of malposition requires a further intervention on the CVAD which implies logistical problems and additional costs. Thus, it is preferable to adopt a method for checking the position of the tip of the CVAD during the placement itself. During catheter insertion, the correct position of the tip can be checked by three different methods: (1) fluoroscopy; (2) trans-thoracic or trans-esophageal echocardiography; and (3) the electrocardiographic method [intracavitary electrocardiography (EKG)]. Many authors have shown that chest X-ray and fluoroscopy are not completely accurate in identifying the post-procedural tip location because "traditional" radiological landmarks of the CAJ are not reliable[34,68,69].

At present, the EKG method is widely employed in Europe (mainly in Germany and Italy) for positioning the tip of VADs[70-73]. The EKG method uses the catheter itself as an intracavitary (endovascular) electrode. If adopting the "column of saline" technique, the method can be applied to any type of CVADs (CICCs, PICCs, dialysis catheters, tunneled-cuffed catheters, ports, *etc.*), both with open-ended or closed ended tip. The electrocardiographic methodology presents several important features: has the same accuracy of the fluoroscopy, however, it is easier to use, more promptly accessible, more secure and, therefore, has a major cost-effectiveness[63,71-76] (Figure 7).

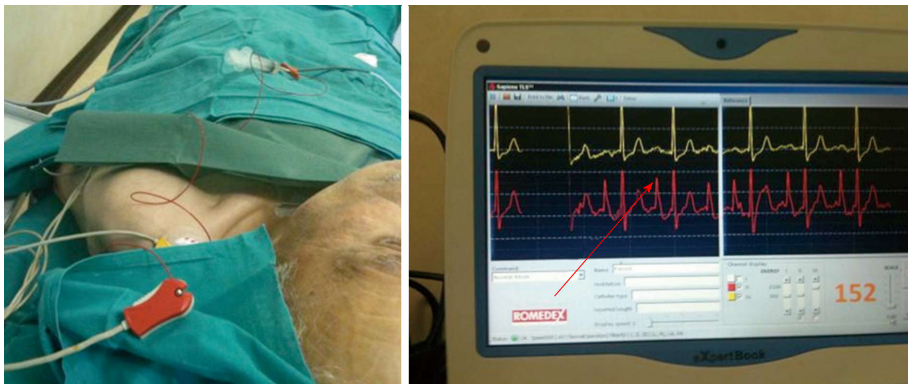


Figure 7 The electrocardiographic method (intracavitary electrocardiography). The red arrow shows the maximal height of *P*-wave detectable when the catheter tip is at cavo-atrial junction (intracavitary EKG = red line, lead Ⅱ). The yellow line is the surface EKG (lead Ⅲ). EKG: Electrocardiography.

CARE OF THE VAD

Care of the CVAD is a crucial issue in critically ill patients and its importance is equal to catheter choice or insertion. CVAD care might be judged a simple procedure, but if strict adherence to guidelines recommendations is not adopted it can lead to even life-threatening harms[44]. In the early years of CVAD, it was shown that the most significant actions to reduce CRBSIs were accurate aseptic care during replace of the dressing and access to the catheter reserved only to specially trained nurses[77]. Nowadays, worldwide registered nurses play a fundamental role in evaluating the need of a VAD in each patient and in preserving the functionality of the device[78]. Moreover, in several countries nursing involvement in CVAD management is highly developed, as specially trained nurses choose and insert both peripheral and central catheters.

It should be highlighted that the risk of CVAD infection is also dependent (in addition to all other well-known factors) on the length of duration (*i.e.*, cumulative risk with each day use). Indeed, the CDC guidelines recommend (Category IA recommendation) the removal of vascular devices that are not necessary as soon as possible[44].

Specific aspects regarding the care of the CVADs lie outside the aim of the present publication; however, their importance is essential. Detailed recommendations are published in literature[43,46], therefore, brief comments about dressing regimens of vascular access exit site, replacement of administration sets, and catheter flushing and locking are reported below.

Dressing of vascular access exit site

Accepted guidelines recommend semi-permeable, sterile, and transparent dressings (*e.g.*, in polyurethane) as a cover of the exit site (see CDC and EPIC guidelines)[40,44]. Transparent dressings permit continuously the vision of the exit site and therefore the frequency of dressing change is reduced if compared to gauzes or other tapes. On the other hand, it is preferable to use gauze dressing in case of diaphoretic patients and of bleeding and oozing from the exit site of catheter[44].

Nevertheless, the choice of dressing is still controversial. Data from a large study about dressing procedures of VADs show that the incidences of colonization or phlebitis of exit sites covered with transparent ones and of those covered with gauze are almost equal[79]. Two meta-analyses have also investigated the CRBSI rate with transparent *vs* gauzes and they found no differences in colonization of skin or catheter tip and bloodstream infections comparing different types of dressing[80,81].

The CDC guidelines recommend replacing dressings of central lines after 48 h for gauzes (Category Ⅱ) and after seven days for transparent ones (Category Ⅰ B), respectively. Indeed, dressing of exit site has to be changed when it is moist, slackened off, or evidently dirty (Category Ⅰ B)[44].

Less debate exists about the utilize of sponge dressing impregnated with chlorhexidine (*i.e.*, a polyurethane scrap with a hole that permits it to fit in the area of the VAD, whose antibacterial activity persists for 7 d). The CDC guidelines recommend the use of these dressing for short term CICCs when the CRBSI rate is still high in spite of adequate "bundles" of CVAD care (Category Ⅰ B). Chlorhexidine-impregnated dressings have been successfully employed for reducing CRBSI rate. In a large RCT in critically ill patients, normal were compared with chlorhexidine dressings showing that CRBSI rates were decreased[82]. However, a meta-analysis of 8 RCTs stated that the use of dressings with chlorhexidine determines a decrease of colonization but without a CRBSI decrease[83]. Although there are few studies investigating the utilize of chlorhexidine-impregnated dressings in children, one RCT showed a reduction of colonization in patients with CVADs covered with chlorhexidine dressings *vs* those with normal ones, but no difference in the CRBSI rate. For this reason, CDC guidelines indicate to do not use the dressings with chlorhexidine in children aged less than two months to avoid contact dermatitis in neonates very small at birth.

The international guidelines[84] stress the need to check regularly the exit site during dressing changes as well as by viewing and palpating the unchanged dressing. In case of local signs (*e.g.*, tenderness) suggesting the infection of the exit site or clinical signs (*e.g.*, fever suggesting a CRBSI) it is mandatory to remove the dressing to allow an accurate exit site inspection (Recommendation: category Ⅰ B).

Administration set replacement

Meta-analyses and several controlled studies investigated the safe and cost-effective interval for routine replacement of all *iv* sets (*i.e.,* those for continuous administration as well as add-on devices and secondary sets). Findings from these studies[85] inspired the CDC guidelines to recommend the substitution of *iv* sets at least 96 h after the beginning of their utilize (Recommendation: category I A). However, new trials suggested that *iv* sets might be utilized in safety for a period up a week whether infusions increasing the growth of pathogens (*e.g.*, blood, plasma, platelets or fat emulsions) have not been administered[86,87]. Conversely, the CDC guidelines recommend replacing every tubing utilized to supply blood, plasma, platelets or lipids (either included in "all-in-one" bags or administered alone) not more than 24 h after the start of the administration (Recommendation: category I B) because they have been recognized as factors significantly associated with an increased risk of CRBSIs[88-91].

Catheter flushing and locking

Flushing the catheter is a basic practice necessary to maintain the patency of any CVAD by reducing drug precipitates and clot formation inside the lumen[92]. Flushing should be done before and after administration of drugs, parenteral nutrition or blood products, after obtaining blood samples, and before locking the device. 10-mL or larger syringes should be preferred, because excessive tension or pressure might harm the CVAD. Flushing protocols in adult patients usually recommend flushing with 10 mL saline in standard conditions (before and after each infusion) and 20 mL saline after infusion of blood products, lipids or contrast medium, or after blood sampling. Flushing should be performed with the so-called push/pause method, *i.e.*, by infusing 2-3 mL at a time.

While a few old meta-analyses investigating the efficacy of heparin on duration of catheter patency had demonstrated some beneficial effect in the 90s[93-95], a more recent review covering a period from 1982 to 2008 did not found strength of evidence to affirm that 0.9% sodium chloride [*i.e.,* normal saline (NS)] is less effective than heparin for flushing CVADs[96]. A recent randomized trial compared heparin and normal saline flush solutions for CICC maintenance in critically ill patients[97]. This study has confirmed that heparin and normal saline flushing solutions have similar rates of lumen occlusion. According to many guidelines[43,46] if CVAD is not in use for less than 8 h the heparin lock is not necessary. The heparin lock might be still be used when specifically recommended by manufacturers, in VADs utilized for hemapheresis and hemodialysis[98].

In conclusion, an adequate flushing using heparin is less essential than locking with NS. Particularly, we stress the key role of flushing both before and after utilize with NS for all CVADs, using the so-called pulsating "push/pause" method associated with a positive pressure technique.

NEONATES, INFANTS, CHILDREN

A CVAD is often required in the pediatric patient in several hospital settings (emergency room, ICU, oncology, hematology, surgery, *etc.*) and for different purposes (parenteral nutrition, chemotherapy, antibiotic or other drug infusions, hemodynamic monitoring, blood withdrawal, hemodialysis/hemapheresis procedures, *etc.*). As in adults, CVADs are needed not only because they are a stable, reliable route of fluid and drug administration, but also because some solutions-vesicant or frequently cause of injury of endothelium-must be administrated in high-flow veins[7,43].

Until few years ago, most CVADs in pediatric patients were placed with the surgical cut-down procedure or with the traditional landmark technique (*i.e.*, "blind technique"). It is now well documented that both techniques have serious limitations and are potentially associated with severe complications[99]. In the past ten years, the availability of US guidance for vein cannulation has completely changed the decision-making in venous access in pediatrics[100-104]. Nevertheless, early it was manifest that the use of US lead to an increased rate of successful insertion (both on the whole and at the initial try), quicker cannulation and a reduced rate of insertion-related adverse events[102,105,106]. In recent years, several studies[100-102,107-110] and meta-analyses[38,105,111] compared the "blind" approach to US-guided approach in pediatric patients and stated that the latter is much more effective and safe. According to the guidelines recommendations, US-guided catheter insertion is recommend as the primary method and not as a subsequent choice or a "salvage" technique in case of failure[99].

Indeed, this skill in pediatrics requires a longer training curve in comparison with that in adult patients[26,99]; however, US-guided insertion is recommended to be utilized when the operator has gained even a minimal experience[106]. However, the CVAD insertion in neonates, infants, and children is a risky operation, even when carried out with US. Thus, there is a strong recommendation for the use of US also after the procedure to immediately identify potentially very dangerous adverse events[106].

A recent paper has described in detail US guidance for CVAD insertion in pediatrics[99]. Hereafter, we briefly described the advantage of US guidance in the different venous access. US-guided venipuncture may be utilized for all VAD insertions in the venous system of: neck (*i.e.*, IJV and external JV); thorax (supraclavicular or infraclavicular area; *i.e.*, brachio-cephalic and subclavian vein); mid-arm (*i.e.*, axillary and cephalic vein; basilic vein and brachial veins); and groin (*i.e.*, femoral and saphenous vein).

Puncture of the IJV in neonates is still challenging and nowadays there are no evidence-based recommendations; however, experts suggest that could be useful to employ US for venipuncture consistently, in everyday practice as well in difficult patients, since US allow location of the vein before the skin puncture and therefore constantly increases the probability of successful CVAD

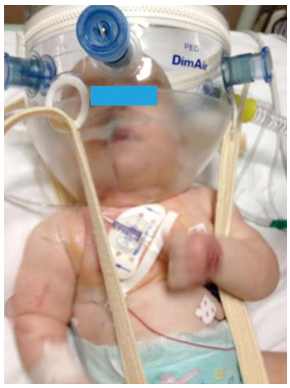


Figure 8 A neonate in intensive care unit with a centrally inserted central catheter.

Figure 9 A children in intensive care unit with a peripherally inserted central catheter.

insertion at the first attempt[26,99].

Usually, US allows the visualization of the subclavian vein all along its course (*i.e.*, from clavicle to brachiocephalic vein)[112]. Two methods are accepted for needle passing: infraclavicular[113] (*i.e.*, passing below the clavicle) and supraclavicular[114] (*i.e.*, above the bone). The infraclavicular approach (Figure 8) offers a wider vision of the SV and, obviously, a catheter exit in the infraclavicular area. The second approach offers perfect needle visualization that is not hampered by the clavicle. In small children, particular attention is needed to visualize the nervous plexus (*i.e.*, brachial)[44].

In infants, US visualization of veins at the groin *(i.e.*, femoral) is usually arduous because in this area the anatomic elements are noticeably less US-detectable in comparison with the neck area[115,116]. The skin puncture for catheter insertion into the FV has to be performed near to inguinal ligament; specifically, the FV lies medial to the common femoral artery). A compression of the low area of the abdomen can be employed to make easy the venipuncture; a thrombosis of the iliac vein may be supposed every time there is no increasing in size[115].

Peripheral venous cannulas are commonly inserted in neonates and children[106]; however, easily may happen that the superficial venous system becomes no more utilizable or an unfeasible venous access is expected. In this case, an US-guided catheter insertion in deeper non visible veins has to be the chosen method[117]; even if, the US visualization of the veins might be complicated due to vein squeeze by the probe[26].

Instead, in the deep veins of the mid-arm (*i.e.*, brachial veins and basilic vein) PICCs may be inserted using US (Figure 9). However, PICCs can be inserted at mid-arm only if the veins of the child are of adequate diameter (at least $\geqslant$ 3 mm). PICCs ($\geqslant$ 3 Fr) are different from the epicutaneo-caval VADs (1-2.7 Fr) which are usually inserted in the superficial veins of neonates. These devices are characterized by very small flow, impossibility of blood withdrawal, and high risk of mechanical complications; their insertion may be facilitated by the use of devices which adopt the Near InfraRed technology, ideal for the visualization of superficial veins.

HEMODIALYSIS CATHETERS

The central venous catheter is a very common access in patients who require the hemodialysis treatment. If it necessary to perform an acute hemodialysis, a non-tunneled and non-cuffed VAD is usually inserted. These catheters are mainly inserted in hospitalized patients with acute renal failure, as well as for a brief period in patients already in chronic hemodialysis that present a failure of their long-term catheters.

VAD complications are the main cause of hospitalization in chronic hemodialysis patients. In particular, central vein stenosis is not an uncommon problem in patients on hemodialysis. Earlier studies reported that subclavian vein stenosis occurs in 15% to 50% of chronic hemodialysis patients[118]. Therefore, the CDC guidelines recommend (Category I A)[44] that acute hemodialysis catheters have to be inserted in the IJV or FV due to the increased possibility of thrombosis and stenosis for catheters inserted into the SV[119].

In the authors' opinion, the risk of venous stenosis after subclavian inserted lines is mostly related to the size of the catheter and to the possible occurrence of a catheter-related thrombosis of the SV (since the stenosis is often the final fibrotic consequence of a severe occlusive thrombosis with only partial recanalization). In our institution, subclavian stenosis is quite rare, since we avoid the placement of large bore dialysis catheter *via* the subclavian route [*i.e.*, we follow the recommendations of the kidney dialysis outcomes quality initiative guidelines for dialysis access][120] and we do our best efforts to insert catheters in veins with inner diameter at least three times the outer diameter of the catheter (of course, this is possible only with a consistent use of US for a pre-puncture evaluation of the vein).

Additionally, some chronic hemodialysis patients may present acutely ill with an indwelling central access devices, such us pre-existing tunneled-cuffed catheters, whereas these devices are the actual source of illness. In these cases, if infection suspect, it is enormously important to remove these devices as soon as possible. In fact, some of these tunneled-cuffed accesses can be removed

at bedside[121].

Finally, the need for dialysis or hemapheresis in the adult critically ill patient is still an absolute indication to a CICC, as no double lumen PICC appears to be useful in this regard. Specific aspects of hemodialysis catheters are beyond the scope of this review, since PICCs have little or no role in this regard. We refer the reader to a comprehensive review on the subject of hemodialysis catheters[122].

STRENGTHS AND LIMITATIONS OF PICCS

In 1996, the first case series of PICCs inserted in critically ill patients was described[123]. However, some technical limitations have limited the introduction of PICCs into daily practice in the ICU because of critically ill patients have special needs (*e.g.*, high flow rates of *iv* infusions; simultaneous administration of potentially incompatible drugs; hemodynamic monitoring).

In the past, valved PICCs have been widely used. They were provided with pressure-sensitive valves to avoid the blood backflow, either distal (close-ended silicon catheters with Groshong valve) or proximal (open-ended polyurethane catheters with pressure safety valve or SOLO valve). More recently, non-valved polyurethane PICCs are becoming increasingly popular also the in critical care setting. In particular, power-injectable open-ended non-valved polyurethane PICCs are preferred in critically ill patients, since they are ideal for delivering high flows (up to 300 mL/min). Moreover, because are open-ended non-valved catheters, these PICCs may be used to monitor central venous pressure (CVP) as well as $ScvO_2$ (central venous oxygen saturation)[124]. Currently, are available both single-lumen (3-5 Fr) and multi-lumen [double lumen (4-5 Fr) and triple lumen (6 Fr)] power-injectable PICCs. These PICCs have the additional advantage of tolerating high-pressure injection (up to 300-350 PSI) of contrast media during radiological procedures, while silicone-made VADs are resistant just about to 50-60 PSI, as standard polyurethane-made VADs up to 100 PSI.

The choice of the material of (silicone *vs* polyurethane PICCs) has been a matter of debate. For long time, the silicone has been regarded has more favorable than polyurethane in terms of biocompatibility and risk of venous thrombosis[125]. Though, more recent investigations have failed to detect any significant difference between silicone and new polyurethanes in terms of risk of infection, risk of thrombosis, or expected dwell time. On the other hand, those polyurethane-made are more preferred than those silicone-made thanks to some characteristics that greatly enhance infusion flow and decrease the rate of dislodgement or fracture of the catheter, such as high resistance to rupture, ample inner diameter, and thin wall. This is particularly true for last generation of ultra-resistant polyurethane power-injectable PICCs.

Pump-driven *iv* infusions may be administered without particular problems through both silicone- and polyurethane-made PICCs, specially using catheters whose diameter is 4 Fr or larger. However, polyurethane-made PICCs are related to a lower incidence of rupture rather than silicone-made PICCs[126]. Moreover, ultra-resistant polyurethane-made power-injectable catheters seems to reduce the rate of occlusion and dislocation more than silicon and standard polyurethane PICCs[127].

Conflicting results about the incidence of CRCs were reported for PICCs in hospitalized patients (principally, in critically ill patients). Two studies in ICU patients with PICCs, one regarding standard ones[128] and another power-injectable ones (three-lumen 6 Fr)[129] have described a high incidence of symptomatic PICC-related thrombosis. Conversely, two other studies in patients with power-injectable PICCs have found a lesser rate of thrombosis ($\leqslant$ 5%)[15,130]. Chopra *et al*[131] in a recent meta-analysis reported a high incidence of PICC-related thrombosis. However, the results of this meta-analysis are difficult to accept because are based on a mixed pool of studies on PICCs of different materials, as well as PICCs inserted both with blind technique and US guidance.

Comparison between CICCs and PICCs

Since the 1970's, in critically ill patients CICCs are inserted in central veins (IJV, SV, axillary, and innominate) for short duration therapy. In the last decade, some authors have proposed PICCs in place of CICCs also in critically ill patients. In fact, PICCs present many theoretical advantages-previously reported in this review-for any hospitalized patient but more relevant in the ICU setting.

Even though this matter is still questionable[3,132], PICCs are generally judged to be less risky for CRBSI, compared with CICCs, which may be an important advantage in ICU patients. This advantage is probably due to the exit site of PICCs, less prone to contamination if compared to the exit sites of CICCs; specifically, the number of bacteria is lower in the skin of upper arms than in the infraclavicular and neck skin[2,40]. Moreover, placement at the upper mid-arm presents the important benefit of removing secretions (nasal, oral, endotracheal) from catheter exit site[2,40]; though, such hypothesis has not yet been proven by RCTs[40]. Finally, a more favorable care of the catheter exit site is obtained by placing PICCs at the upper mid-arm[27]. Indeed, accepted guidelines suggest that PICC may be taken into account as the first option in tracheostomy patients[7].

In a large trial on CVADs in critically ill patients, CICCs were related to a relevant higher incidence of CRBSIs compared to PICCs[133]. Three recent papers in ICU patients reported a CRBSI rate equal to zero[15,129,134]. The hypothesis regarding a lower risk of CRBSI with PICCs than CICCs should be demonstrated by appropriately designed RCTs[135]. With regards to critically ill patients, at present there are not available evidence-based data showing clear advantages of PICCs *vs* CICCs, or viceversa.

Summarizing, the rate of VAD-related complications, as well the expected dwell time of a CVAD (CICC or PICC) depend on several factors: right ratio between vein

and catheter diameter, technique of insertion (US guidance *vs* blind technique), proper tip position, appropriate exit site location, catheter securement technique (sutureless devices *vs* sutures), patient's compliance, and, last but not least, the competence of nurses in the maintenance policies.

CONCLUSION

Two important take-home messages may be drawn from this review. First, the incidence of CRCs is different between different CVADs and physicians should be aware of the different clinical performance as well as of the different risks associated with each type of CVAD (CICCs or PICCs). Second, an inappropriate CVAD choice and, particularly, an inadequate insertion technique are relevant -and often not recognized- potential risk factors for complications in critically ill patients.

We strongly believe that all health-care professionals involved in the choice, insertion or management of CVADs in critically ill patients should know all potential risk factors of CRCs. This knowledge may yield to minimize complications and guarantee longevity to the CVAD optimizing the risk/benefit ratio of CVAD insertion and use. Summarizing, the proper care of CVADs in critical care save lines and save lives.

In conclusion, much evidence from the medical literature and from the clinical practice supports the belief that polyurethane-made power-injectable PICCs may be considered a convincing choice in critical care. Certainly, RCTs comparing CICCs with PICCs are mandatory for recommendations on CVAD choice in critically ill patients.

REFERENCES

1 **Barton AJ**, Danek G, Johns P, Coons M. Improving patient outcomes through CQI: vascular access planning. *J Nurs Care Qual* 1998; **13**: 77-85 [PMID: 9842178 DOI: 10.1097/00001786-199812000-00010]

2 **Ryder MA**. Peripheral access options. *Surg Oncol Clin N Am* 1995; **4**: 395-427 [PMID: 7552784]

3 **Maki DG**, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc* 2006; **81**: 1159-1171 [PMID: 16970212 DOI: 10.4065/81.9.1159]

4 Million Lives Campaign. Getting Started Kit: Prevent Central Line Infections How-to Guide. Cambridge, MA: Institute for Healthcare Improvement (IHI). Available from: URL: http://www.ihi.org/

5 **Bozzetti F**, Mariani L, Bertinet DB, Chiavenna G, Crose N, De Cicco M, Gigli G, Micklewright A, Moreno Villares JM, Orban A, Pertkiewicz M, Pironi L, Vilas MP, Prins F, Thul P. Central venous catheter complications in 447 patients on home parenteral nutrition: an analysis of over 100.000 catheter days. *Clin Nutr* 2002; **21**: 475-485 [PMID: 12468367 DOI: 10.1054/clnu.2002.0578]

6 **Beghetto MG**, Victorino J, Teixeira L, de Azevedo MJ. Parenteral nutrition as a risk factor for central venous catheter-related infection. *JPEN J Parenter Enteral Nutr* 2005; **29**: 367-373 [PMID: 16107600 DOI: 10.1177/0148607105029005367]

7 **Pittiruti M**, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr* 2009; **28**: 365-377 [PMID: 19464090 DOI: 10.1016/j.clnu.2009.04.004]

8 **Gallieni M**, Pittiruti M, Biffi R. Vascular access in oncology patients. *CA Cancer J Clin* 2008; **58**: 323-346 [PMID: 18971486 DOI: 10.3322/CA.2008.0015]

9 **Kuwahara T**, Asanami S, Kubo S. Experimental infusion phlebitis: tolerance osmolality of peripheral venous endothelial cells. *Nutrition* 1998; **14**: 496-501 [PMID: 9646289 DOI: 10.1016/S0899-9007(98)00037-9]

10 **Isaacs JW**, Millikan WJ, Stackhouse J, Hersh T, Rudman D. Parenteral nutrition of adults with a 900 milliosmolar solution via peripheral veins. *Am J Clin Nutr* 1977; **30**: 552-559 [PMID: 403755]

11 **Palmer D**, McFie J. Venous access for parenteral nutrition. In: Payne James J, Grimble GK, Silk, DBA. Artificial nutrition support in clinical practice. London, UK, 2001: 379-400

12 **Ryder M**. Evidence-based practice in the management of vascular access devices for home parenteral nutrition therapy. *JPEN J Parenter Enteral Nutr* 2006; **30**: S82-S93, S98-S99 [PMID: 16387917]

13 **Cotogni P**, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-related complications in cancer patients on home parenteral nutrition: a prospective study of over 51,000 catheter days. *JPEN J Parenter Enteral Nutr* 2013; **37**: 375-383 [PMID: 23002096 DOI: 10.1177/0148607112460552]

14 **Griffiths VR**, Philpot P. Peripherally inserted central catheters (PICCs): do they have a role in the care of the critically ill patient? *Intensive Crit Care Nurs* 2002; **18**: 37-47 [PMID: 12008876 DOI: 10.1054/iccn.2002.1615]

15 **Pittiruti M**, Brutti A, Celentano D, Pomponi M, Biasucci DG, Annetta MG, Scoppettuolo G. Clinical experience with power-injectable PICCs in intensive care patients. *Crit Care* 2012; **16**: R21 [PMID: 22305301 DOI: 10.1186/cc11181]

16 **Macdonald S**, Watt AJ, McNally D, Edwards RD, Moss JG. Comparison of technical success and outcome of tunneled catheters inserted via the jugular and subclavian approaches. *J Vasc Interv Radiol* 2000; **11**: 225-231 [PMID: 10716395 DOI: 10.1016/S1051-0443(07)61470-5]

17 **Pittiruti M**, Malerba M, Carriero C, Tazza L, Gui D. Which is the easiest and safest technique for central venous access? A retrospective survey of more than 5,400 cases. *J Vasc Access* 2000; **1**: 100-107 [PMID: 17638235]

18 **Harden JL**, Kemp L, Mirtallo J. Femoral catheters increase risk of infection in total parenteral nutrition patients. *Nutr Clin Pract* 1995; **10**: 60-66 [PMID: 7731426 DOI: 10.1177/011542659501000260]

19 **McGee DC**, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003; **348**: 1123-1133 [PMID: 12646670 DOI: 10.1056/NEJMra011883]

20 **Merrer J**, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, Rigaud JP, Casciani D, Misset B, Bosquet C, Outin H, Brun-Buisson C, Nitenberg G. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001; **286**: 700-707 [PMID: 11495620 DOI: 10.1001/jama.286.6.700]

21 **Hamilton HC**, Foxcroft DR. Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy. *Cochrane Database Syst Rev* 2007; (**3**): CD004084 [PMID: 17636746 DOI: 10.1002/14651858CD004084]

22 **Araújo C**, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, Dias T, Fougo JL. A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. *Eur J Surg Oncol* 2008; **34**: 222-226 [PMID: 17566692 DOI: 10.1016/j.ejso.2007.04.003]

23 **Marik PE**, Flemmer M, Harrison W. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis.

Crit Care Med 2012; **40**: 2479-2485 [PMID: 22809915 DOI: 10.1097/CCM.0b013e318255d9bc]
24 **Lorente L**, Villegas J, Martín MM, Jiménez A, Mora ML. Catheter-related infection in critically ill patients. *Intensive Care Med* 2004; **30**: 1681-1684 [PMID: 15160239 DOI: 10.1007/s00134-004-2332-3]
25 **Deshpande KS**, Hatem C, Ulrich HL, Currie BP, Aldrich TK, Bryan-Brown CW, Kvetan V. The incidence of infectious complications of central venous catheters at the subclavian, internal jugular, and femoral sites in an intensive care unit population. *Crit Care Med* 2005; **33**: 13-20; discussion 234-235 [PMID: 15644643 DOI: 10.1097/01.CCM.0000149838.47048.60]
26 **Lamperti M**, Bodenham AR, Pittiruti M, Blaivas M, Augoustides JG, Elbarbary M, Pirotte T, Karakitsos D, Ledonne J, Doniger S, Scoppettuolo G, Feller-Kopman D, Schummer W, Biffi R, Desruennes E, Melniker LA, Verghese ST. International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Med* 2012; **38**: 1105-1117 [PMID: 22614241 DOI: 10.1007/s00134-012-2597-x]
27 **Pittiruti M**, Migliorini I, Emoli A, Dolcetti L, Pomponi M, Scoppettuolo G, LaGreca A. Preventing central venous catheter related infections: catheter site selection and insertion technique significantly affect the chances of adequate catheter site care. *Intensive Care Med* 2007; **33** Suppl: S13. Available from: URL: http: //icmjournal.esicm.org/index.html
28 **Debourdeau P**, Kassab Chahmi D, Le Gal G, Kriegel I, Desruennes E, Douard MC, Elalamy I, Meyer G, Mismetti P, Pavic M, Scrobohaci ML, Lévesque H, Renaudin JM, Farge D. 2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer: report from the working group. *Ann Oncol* 2009; **20**: 1459-1471 [PMID: 19525362 DOI: 10.1093/annonc/mdp052]
29 **Campisi C**, Biffi R, Pittiruti M; GAVeCeLT Committee for the Consensus. Catheter-related central venous thrombosis-the development of a nationwide consensus paper in Italy. *JAVA* 2007; **12**: 38-46 [DOI: 10.2309/java.12-1-10]
30 **Maecken T**, Grau T. Ultrasound imaging in vascular access. *Crit Care Med* 2007; **35**: S178-S185 [PMID: 17446777 DOI: 10.1097/01.CCM.0000260629.86351.A5]
31 **Kumar A**, Chuan A. Ultrasound guided vascular access: efficacy and safety. *Best Pract Res Clin Anaesthesiol* 2009; **23**: 299-311 [PMID: 19862889 DOI: 10.1016/j.bpa.2009.02.006]
32 **Chapman GA**, Johnson D, Bodenham AR. Visualisation of needle position using ultrasonography. *Anaesthesia* 2006; **61**: 148-158 [PMID: 16430568 DOI: 10.1111/j.1365-2044.2005.04475.x]
33 **Ortega R**, Song M, Hansen CJ, Barash P. Videos in clinical medicine. Ultrasound-guided internal jugular vein cannulation. *N Engl J Med* 2010; **362**: e57 [PMID: 20410510 DOI: 10.1056/NEJMvcm0810156]
34 **Hsu JH**, Wang CK, Chu KS, Cheng KI, Chuang HY, Jaw TS, Wu JR. Comparison of radiographic landmarks and the echocardiographic SVC/RA junction in the positioning of long-term central venous catheters. *Acta Anaesthesiol Scand* 2006; **50**: 731-735 [PMID: 16987369]
35 **Serafimidis K**, Sakorafas GH, Konstantoudakis G, Petropoulou K, Giannopoulos GP, Danias N, Peros G, Safioleas M. Ultrasound-guided catheterization of the internal jugular vein in oncologic patients; comparison with the classical anatomic landmark technique: a prospective study. *Int J Surg* 2009; **7**: 526-528 [PMID: 19751852 DOI: 10.1016/j.ijsu.2009.08.011]
36 **Randolph AG**, Cook DJ, Gonzales CA, Pribble CG. Ultrasound guidance for placement of central venous catheters: a meta-analysis of the literature. *Crit Care Med* 1996; **24**: 2053-2058 [PMID: 8968276 DOI: 10.1097/00003246-199612000-00020]
37 **Shojania KG**, Duncan BW, McDonald KM, Wachter RM, Markowitz AJ. Making Health Care Safer. A Critical Analysis of Patient Safety Practices: Summary. July 2001. AHRQ Publication No. 01-E057. Rockville, MD: Agency for Healthcare Research and Quality. Available from: URL: http: //www.ahrq.gov/clinic/ptsafety/summary.htm
38 **Hind D**, Calvert N, McWilliams R, Davidson A, Paisley S, Beverley C, Thomas S. Ultrasonic locating devices for central venous cannulation: meta-analysis. *BMJ* 2003; **327**: 361 [PMID: 12919984 DOI: 10.1136/bmj.327.7411.361]
39 **Calvert N**, Hind D, McWilliams R, Davidson A, Beverley CA, Thomas SM. Ultrasound for central venous cannulation: economic evaluation of cost-effectiveness. *Anaesthesia* 2004; **59**: 1116-1120 [PMID: 15479322 DOI: 10.1111/j.1365-2044.2004.03906.x]
40 **Loveday HP**, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, Browne J, Prieto J, Wilcox M. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014; **86 Suppl 1**: S1-70 [PMID: 24330862 DOI: 10.1016/S0195-6701(13)60012-2]
41 **Marschall J**, Mermel LA, Classen D, Arias KM, Podgorny K, Anderson DJ, Burstin H, Calfee DP, Coffin SE, Dubberke ER, Fraser V, Gerding DN, Griffin FA, Gross P, Kaye KS, Klompas M, Lo E, Nicolle L, Pegues DA, Perl TM, Saint S, Salgado CD, Weinstein RA, Wise R, Yokoe DS. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008; **29** Suppl 1: S22-S30 [PMID: 18840085 DOI: 10.1086/591059]
42 **Mermel LA**, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1-45 [PMID: 19489710 DOI: 10.1086/599376]
43 **INS 2011**. Infusion nursing standards of practice developed by Infusion Nurses Society. *INS* 2011; **34**: S1-S109. Available from: URL: http: //www.ins1.org
44 **O'Grady NP**, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011; **39**: S1-34 [PMID: 21511081 DOI: 10.1016/j.ajic.2011.01.003]
45 **National Institute for Clinical Excellence (NICE)**. Guidance on the use of ultrasound locating devices for placing central venous catheters. 2002. Available from: URL: http: //www.nice.org.uk
46 **Royal College of Nursing (RCN)**. I.V. Therapy Forum: Standards for Infusion Therapy. 2010. Available from: URL: http: //www.rcn.org.uk
47 **American College of Surgeons (ACS)**. Statement on recommendations for uniform use of real-time ultrasound guidance for placement of central venous catheters. 2008. Available from: URL: http: //www.facs.org/fellows_info/statements/st-60html
48 **Association for Vascular Access (AVA)**. Position Statement on the Use of Real-Time Imaging Modalities for Placement of Central Venous Access Devices. 2008. Available from: URL: http: //www.avainfo.org
49 **British Committee for Standards in Haematology (BCSH)**. Guidelines on the insertion and management of central venous access devices in adults. 2006. Available from: URL: http: //www.evanetwork.info
50 **Leung J**, Duffy M, Finckh A. Real-time ultrasonographically-guided internal jugular vein catheterization in the emergency department increases success rates and reduces complications: a randomized, prospective study. *Ann Emerg Med* 2006; **48**: 540-547 [PMID: 17052555]
51 **Augoustides JG**, Horak J, Ochroch AE, Vernick WJ, Gambone AJ, Weiner J, Pinchasik D, Kowalchuk D, Savino JS, Jobes DR. A randomized controlled clinical trial of real-time needle-guided ultrasound for internal jugular venous can-

nulation in a large university anesthesia department. *J Cardiothorac Vasc Anesth* 2005; **19**: 310-315 [PMID: 16130056 DOI: 10.1053/j.jvca.2005.03.007]
52 **French JL**, Raine-Fenning NJ, Hardman JG, Bedforth NM. Pitfalls of ultrasound guided vascular access: the use of three/four-dimensional ultrasound. *Anaesthesia* 2008; **63**: 806-813 [PMID: 18549414 DOI: 10.1111/j.1365-2044.2008.05513.x]
53 **Blaivas M**, Adhikari S. An unseen danger: frequency of posterior vessel wall penetration by needles during attempts to place internal jugular vein central catheters using ultrasound guidance. *Crit Care Med* 2009; **37**: 2345-2349; quiz 2359 [PMID: 19531950 DOI: 10.1097/CCM.0b013e3181a067d4]
54 **Bodenham AR**. Can you justify not using ultrasound guidance for central venous access? *Crit Care* 2006; **10**: 175 [PMID: 17129362 DOI: 10.1186/cc5079]
55 **Farkas JC**, Liu N, Bleriot JP, Chevret S, Goldstein FW, Carlet J. Single- versus triple-lumen central catheter-related sepsis: a prospective randomized study in a critically ill population. *Am J Med* 1992; **93**: 277-282 [PMID: 1524079 DOI: 10.1016/0002-9343(92)90233-2]
56 **Dezfulian C**, Lavelle J, Nallamothu BK, Kaufman SR, Saint S. Rates of infection for single-lumen versus multilumen central venous catheters: a meta-analysis. *Crit Care Med* 2003; **31**: 2385-2390 [PMID: 14501971 DOI: 10.1097/01.CCM.0000084843.31852.01]
57 **Zürcher M**, Tramèr MR, Walder B. Colonization and bloodstream infection with single- versus multi-lumen central venous catheters: a quantitative systematic review. *Anesth Analg* 2004; **99**: 177-182 [PMID: 15281526 DOI: 10.1213/01.ANE.0000118101.94596.A0]
58 **Bishop L**, Dougherty L, Bodenham A, Mansi J, Crowe P, Kibbler C, Shannon M, Treleaven J. Guidelines on the insertion and management of central venous access devices in adults. *Int J Lab Hematol* 2007; **29**: 261-278 [PMID: 17617077 DOI: 10.1111/j.1751-553X.2007.00931.x]
59 **Vesely TM**. Central venous catheter tip position: a continuing controversy. *J Vasc Interv Radiol* 2003; **14**: 527-534 [PMID: 12761305 DOI: 10.1097/01.RVI.0000071097.76348.72]
60 **National Association of Vascular Access Networks**. NAVAN position statement on terminal tip placement. *J Vascular Access Dev* 1998; **3**: 8-10
61 **Scott WL**. Complications associated with central venous catheters. A survey. *Chest* 1988; **94**: 1221-1224 [PMID: 3191763 DOI: 10.1378/chest.94.6.1221]
62 **Scott WL**. Central venous catheters. An overview of Food and Drug Administration activities. *Surg Oncol Clin N Am* 1995; **4**: 377-393 [PMID: 7552783]
63 **Pittiruti M**, La Greca A, Scoppettuolo G. The electrocardiographic method for positioning the tip of central venous catheters. *J Vasc Access* 2011; **12**: 280-291 [PMID: 21667458 DOI: 10.5301/JVA.2011.8381]
64 **Petersen J**, Delaney JH, Brakstad MT, Rowbotham RK, Bagley CM. Silicone venous access devices positioned with their tips high in the superior vena cava are more likely to malfunction. *Am J Surg* 1999; **178**: 38-41 [PMID: 10456700 DOI: 10.1016/S0002-9610(99)00124-5]
65 **Caers J**, Fontaine C, Vinh-Hung V, De Mey J, Ponnet G, Oost C, Lamote J, De Greve J, Van Camp B, Lacor P. Catheter tip position as a risk factor for thrombosis associated with the use of subcutaneous infusion ports. *Support Care Cancer* 2005; **13**: 325-331 [PMID: 15538639 DOI: 10.1007/s00520-004-0723-1]
66 **Taylor RW**, Palagiri AV. Central venous catheterization. *Crit Care Med* 2007; **35**: 1390-1396 [PMID: 17414086 DOI: 10.1097/01.CCM.0000260241.80346.1B]
67 **Korones DN**, Buzzard CJ, Asselin BL, Harris JP. Right atrial thrombi in children with cancer and indwelling catheters. *J Pediatr* 1996; **128**: 841-846 [PMID: 8648545 DOI: 10.1016/S0022-3476(96)70338-4]
68 **Aslamy Z**, Dewald CL, Heffner JE. MRI of central venous anatomy: implications for central venous catheter insertion. *Chest* 1998; **114**: 820-826 [PMID: 9743173 DOI: 10.1378/chest.114.3.820]
69 **Wirsing M**, Schummer C, Neumann R, Steenbeck J, Schmidt P, Schummer W. Is traditional reading of the bedside chest radiograph appropriate to detect intraatrial central venous catheter position? *Chest* 2008; **134**: 527-533 [PMID: 18641117 DOI: 10.1378/chest.07-2687]
70 **Chu KS**, Hsu JH, Wang SS, Tang CS, Cheng KI, Wang CK, Wu JR. Accurate central venous port-A catheter placement: intravenous electrocardiography and surface landmark techniques compared by using transesophageal echocardiography. *Anesth Analg* 2004; **98**: 910-914, table of contents [PMID: 15041571 DOI: 10.1213/01.ANE.0000105865.94157.4C]
71 **Gebhard RE**, Szmuk P, Pivalizza EG, Melnikov V, Vogt C, Warters RD. The accuracy of electrocardiogram-controlled central line placement. *Anesth Analg* 2007; **104**: 65-70 [PMID: 17179244 DOI: 10.1213/01.ane.0000250224.02440.fe]
72 **Antonaglia V**, Ristagno G, Berlot G. Procedural and clinical data plus electrocardiographic guidance greatly reduce the need for routine chest radiograph following central line placement. *J Trauma* 2008; **64**: 1146 [PMID: 18404090 DOI: 10.1097/TA.0b013e31815dd4ea]
73 **David JS**, Tazarourte K, Perfus JP, Savary D. Is ECG-guidance a helpful method to correctly position a central venous catheter during prehospital emergency care? *Acta Anaesthesiol Scand* 2005; **49**: 1010-1014 [PMID: 16045664 DOI: 10.1111/j.1399-6576.2005.00762.x]
74 **Madias JE**. Intracardiac (superior vena cava/right atrial) ECGs using saline solution as the conductive medium for the proper positioning of the Shiley hemodialysis catheter: is it not time to forego [correction of forgo] the postinsertion chest radiograph? *Chest* 2003; **124**: 2363-2367 [PMID: 14665521 DOI: 10.1378/chest.124.6.2363]
75 **Pittiruti M**, Scoppettuolo G, La Greca A, Emoli A, Brutti A, Migliorini I, Dolcetti L, Taraschi C, DePascale G. The EKG method for positioning the tip of PICCs: results from two preliminary studies. *JAVA* 2008; **13**: 112-119 [DOI: 10.2309/java.13-4-4]
76 **Pittiruti M**, Bertollo D, Briglia E, Buononato M, Capozzoli G, De Simone L, La Greca A, Pelagatti C, Sette P. The intracavitary ECG method for positioning the tip of central venous catheters: results of an Italian multicenter study. *J Vasc Access* 2012; **13**: 357-365 [PMID: 22328361 DOI: 10.5301/JVA.2012.9020]
77 **Keohane PP**, Jones BJ, Attrill H, Cribb A, Northover J, Frost P, Silk DB. Effect of catheter tunnelling and a nutrition nurse on catheter sepsis during parenteral nutrition. A controlled trial. *Lancet* 1983; **2**: 1388-1390 [PMID: 6140494 DOI: 10.1016/S0140-6736(83)90922-4]
78 **Arch P**. Port navigation: let the journey begin. *Clin J Oncol Nurs* 2007; **11**: 485-488 [PMID: 17723960 DOI: 10.1188/07.CJON.485-488]
79 **Maki DG**, Ringer M. Evaluation of dressing regimens for prevention of infection with peripheral intravenous catheters. Gauze, a transparent polyurethane dressing, and an iodophor-transparent dressing. *JAMA* 1987; **258**: 2396-2403 [PMID: 3118061 DOI: 10.1001/jama.1987.03400170082027]
80 **Hoffmann KK**, Weber DJ, Samsa GP, Rutala WA. Transparent polyurethane film as an intravenous catheter dressing. A meta-analysis of the infection risks. *JAMA* 1992; **267**: 2072-2076 [PMID: 1532429 DOI: 10.1001/jama.267.15.2072]
81 **Gillies D**, O'Riordan E, Carr D, O'Brien I, Frost J, Gunning R. Central venous catheter dressings: a systematic review. *J Adv Nurs* 2003; **44**: 623-632 [PMID: 14651685 DOI: 10.1046/j.0309-2402.2003.02852.x]
82 **Timsit JF**, Schwebel C, Bouadma L, Geffroy A, Garrouste-Orgeas M, Pease S, Herault MC, Haouache H, Calvino-Gunther S, Gestin B, Armand-Lefevre L, Leflon V, Chaplain C, Benali A, Francais A, Adrie C, Zahar JR, Thuong M, Arrault

X, Croize J, Lucet JC. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA* 2009; **301**: 1231-1241 [PMID: 19318651 DOI: 10.1001/jama.2009.376]

83 **Ho KM**, Litton E. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother* 2006; **58**: 281-287 [PMID: 16757502 DOI: 10.1093/jac/dkl234]

84 **Garland JS**, Alex CP, Mueller CD, Otten D, Shivpuri C, Harris MC, Naples M, Pellegrini J, Buck RK, McAuliffe TL, Goldmann DA, Maki DG. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics* 2001; **107**: 1431-1436 [PMID: 11389271 DOI: 10.1542/peds.107.6.1431]

85 **Gillies D**, O'Riordan L, Wallen M, Morrison A, Rankin K, Nagy S. Optimal timing for intravenous administration set replacement. *Cochrane Database Syst Rev* 2005; (**4**): CD003588 [PMID: 16235329]

86 **Raad I**, Hanna HA, Awad A, Alrahwan A, Bivins C, Khan A, Richardson D, Umphrey JL, Whimbey E, Mansour G. Optimal frequency of changing intravenous administration sets: is it safe to prolong use beyond 72 hours? *Infect Control Hosp Epidemiol* 2001; **22**: 136-139 [PMID: 11310690 DOI: 10.1086/501879]

87 **Rickard CM**, Lipman J, Courtney M, Siversen R, Daley P. Routine changing of intravenous administration sets does not reduce colonization or infection in central venous catheters. *Infect Control Hosp Epidemiol* 2004; **25**: 650-655 [PMID: 15357156]

88 **Melly MA**, Meng HC, Schaffner W. Microbiol growth in lipid emulsions used in parenteral nutrition. *Arch Surg* 1975; **110**: 1479-1481 [PMID: 982 DOI: 10.1001/archsurg.1975.01360180049010]

89 **Mershon J**, Nogami W, Williams JM, Yoder C, Eitzen HE, Lemons JA. Bacterial/fungal growth in a combined parenteral nutrition solution. *JPEN J Parenter Enteral Nutr* 1986; **10**: 498-502 [PMID: 3093707 DOI: 10.1177/014860718601000549 8]

90 **Gilbert M**, Gallagher SC, Eads M, Elmore MF. Microbial growth patterns in a total parenteral nutrition formulation containing lipid emulsion. *JPEN J Parenter Enteral Nutr* 1986; **10**: 494-497 [PMID: 3093706 DOI: 10.1177/0148607186010005494]

91 **Maki DG**, Martin WT. Nationwide epidemic of septicemia caused by contaminated infusion products. IV. Growth of microbial pathogens in fluids for intravenous infusions. *J Infect Dis* 1975; **131**: 267-272 [PMID: 236343 DOI: 10.1093/infdis/131.3.267]

92 **Vescia S**, Baumgärtner AK, Jacobs VR, Kiechle-Bahat M, Rody A, Loibl S, Harbeck N. Management of venous port systems in oncology: a review of current evidence. *Ann Oncol* 2008; **19**: 9-15 [PMID: 17846025 DOI: 10.1093/annonc/mdm272]

93 **Randolph AG**, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. *BMJ* 1998; **316**: 969-975 [PMID: 9550955 DOI: 10.1136/bmj.316.7136.969]

94 **Goode CJ**, Titler M, Rakel B, Ones DS, Kleiber C, Small S, Triolo PK. A meta-analysis of effects of heparin flush and saline flush: quality and cost implications. *Nurs Res* 1991; **40**: 324-330 [PMID: 1835537 DOI: 10.1097/00006199-199111000-00002]

95 **Peterson FY**, Kirchhoff KT. Analysis of the research about heparinized versus nonheparinized intravascular lines. *Heart Lung* 1991; **20**: 631-640 [PMID: 1835721]

96 **Mitchell MD**, Anderson BJ, Williams K, Umscheid CA. Heparin flushing and other interventions to maintain patency of central venous catheters: a systematic review. *J Adv Nurs* 2009; **65**: 2007-2021 [PMID: 20568318 DOI: 10.1111/j.1365-2648.2009.05103.x]

97 **Schallom ME**, Prentice D, Sona C, Micek ST, Skrupky LP. Heparin or 0.9% sodium chloride to maintain central venous catheter patency: a randomized trial. *Crit Care Med* 2012; **40**: 1820-1826 [PMID: 22488006 DOI: 10.1097/CCM.0b013e31824e11b4]

98 **Kuo YS**, Schwartz B, Santiago J, Anderson PS, Fields AL, Goldberg GL. How often should a port-A-cath be flushed? *Cancer Invest* 2005; **23**: 582-585 [PMID: 16305984 DOI: 10.1080/07357900500276923]

99 **Pittiruti M**. Ultrasound guided central vascular access in neonates, infants and children. *Curr Drug Targets* 2012; **13**: 961-969 [PMID: 22512396 DOI: 10.2174/138945012800675696]

100 **Verghese ST**, McGill WA, Patel RI, Sell JE, Midgley FM, Ruttimann UE. Comparison of three techniques for internal jugular vein cannulation in infants. *Paediatr Anaesth* 2000; **10**: 505-511 [PMID: 11012954 DOI: 10.1046/j.1460-9592.2000.00554.x]

101 **Verghese ST**, McGill WA, Patel RI, Sell JE, Midgley FM, Ruttimann UE. Ultrasound-guided internal jugular venous cannulation in infants: a prospective comparison with the traditional palpation method. *Anesthesiology* 1999; **91**: 71-77 [PMID: 10422930 DOI: 10.1097/00000542-199907000-00013]

102 **Lamperti M**, Caldiroli D, Cortellazzi P, Vailati D, Pedicelli A, Tosi F, Piastra M, Pietrini D. Safety and efficacy of ultrasound assistance during internal jugular vein cannulation in neurosurgical infants. *Intensive Care Med* 2008; **34**: 2100-2105 [PMID: 18618096 DOI: 10.1007/s00134-008-1210-9]

103 **Milling T**, Holden C, Melniker L, Briggs WM, Birkhahn R, Gaeta T. Randomized controlled trial of single-operator vs. two-operator ultrasound guidance for internal jugular central venous cannulation. *Acad Emerg Med* 2006; **13**: 245-247 [PMID: 16495416 DOI: 10.1111/j.1553-2712.2006.tb01686.x]

104 **Mallinson C**, Bennett J, Hodgson P, Petros AJ. Position of the internal jugular vein in children. A study of the anatomy using ultrasonography. *Paediatr Anaesth* 1999; **9**: 111-114 [PMID: 10189649 DOI: 10.1046/j.1460-9592.1999.9220329.x]

105 **Sigaut S**, Skhiri A, Stany I, Golmar J, Nivoche Y, Constant I, Murat I, Dahmani S. Ultrasound guided internal jugular vein access in children and infant: a meta-analysis of published studies. *Paediatr Anaesth* 2009; **19**: 1199-1206 [PMID: 19863734 DOI: 10.1111/j.1460-9592.2009.03171.x]

106 **Detaille T**, Pirotte T, Veyckemans F. Vascular access in the neonate. *Best Pract Res Clin Anaesthesiol* 2010; **24**: 403-418 [PMID: 21033016 DOI: 10.1016/j.bpa.2010.02.017]

107 **Asheim P**, Mostad U, Aadahl P. Ultrasound-guided central venous cannulation in infants and children. *Acta Anaesthesiol Scand* 2002; **46**: 390-392 [PMID: 11952438 DOI: 10.1034/j.1399-6576.2002.460410.x]

108 **Froehlich CD**, Rigby MR, Rosenberg ES, Li R, Roerig PL, Easley KA, Stockwell JA. Ultrasound-guided central venous catheter placement decreases complications and decreases placement attempts compared with the landmark technique in patients in a pediatric intensive care unit. *Crit Care Med* 2009; **37**: 1090-1096 [PMID: 19237922 DOI: 10.1097/CCM.0b013e31819b570e]

109 **Hosokawa K**, Shime N, Kato Y, Hashimoto S. A randomized trial of ultrasound image-based skin surface marking versus real-time ultrasound-guided internal jugular vein catheterization in infants. *Anesthesiology* 2007; **107**: 720-724 [PMID: 18073546 DOI: 10.1097/01.anes.0000287024.19704.96]

110 **Leyvi G**, Taylor DG, Reith E, Wasnick JD. Utility of ultrasound-guided central venous cannulation in pediatric surgical patients: a clinical series. *Paediatr Anaesth* 2005; **15**: 953-958 [PMID: 16238556 DOI: 10.1111/j.1460-9592.2005.01609.x]

111 **Patil V**, Jaggar S. Ultrasound guided internal jugular vein access in children and infant: a meta-analysis. *Paediatr Anaesth* 2010; **20**: 474-475 [PMID: 20519013 DOI: 10.1111/j.1460-9592.2010.03283.x]

112 **Breschan C**, Platzer M, Jost R, Stettner H, Likar R. Size of internal jugular vs subclavian vein in small infants: an observational, anatomical evaluation with ultrasound. *Br J Anaesth* 2010; **105**: 179-184 [PMID: 20542889 DOI: 10.1093/bja/aeq123]

113 **Pirotte T**, Veyckemans F. Ultrasound-guided subclavian vein cannulation in infants and children: a novel approach. *Br J Anaesth* 2007; **98**: 509-514 [PMID: 17332002 DOI: 10.1093/bja/aem041]

114 **Rhondali O**, Attof R, Combet S, Chassard D, de Queiroz Siqueira M. Ultrasound-guided subclavian vein cannulation in infants: supraclavicular approach. *Paediatr Anaesth* 2011; **21**: 1136-1141 [PMID: 21627714 DOI: 10.1111/j.1460-9592.2011.03614.x]

115 **Iwashima S**, Ishikawa T, Ohzeki T. Ultrasound-guided versus landmark-guided femoral vein access in pediatric cardiac catheterization. *Pediatr Cardiol* 2008; **29**: 339-342 [PMID: 17851631]

116 **Hopkins JW**, Warkentine F, Gracely E, Kim IK. The anatomic relationship between the common femoral artery and common femoral vein in frog leg position versus straight leg position in pediatric patients. *Acad Emerg Med* 2009; **16**: 579-584 [PMID: 19519804 DOI: 10.1111/j.1553-2712.2009.00430.x]

117 **Doniger SJ**, Ishimine P, Fox JC, Kanegaye JT. Randomized controlled trial of ultrasound-guided peripheral intravenous catheter placement versus traditional techniques in difficult-access pediatric patients. *Pediatr Emerg Care* 2009; **25**: 154-159 [PMID: 19262420 DOI: 10.1097/PEC.0b013e31819a8946]

118 **Hernández D**, Díaz F, Rufino M, Lorenzo V, Pérez T, Rodríguez A, De Bonis E, Losada M, González-Posada JM, Torres A. Subclavian vascular access stenosis in dialysis patients: natural history and risk factors. *J Am Soc Nephrol* 1998; **9**: 1507-1510 [PMID: 9697674]

119 **Oliver MJ**. Acute dialysis catheters. *Semin Dial* 2001; **14**: 432-435 [PMID: 11851928 DOI: 10.1046/j.1525-139x.2001.00107.x]

120 **Vascular Access 2006 Work Group**. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; **48** Suppl 1: S176-S247 [PMID: 16813989]

121 **Fülöp T**, Tapolyai M, Qureshi NA, Beemidi VR, Gharaibeh KA, Hamrahian SM, Szarvas T, Kovesdy CP, Csongrádi E. The safety and efficacy of bedside removal of tunneled hemodialysis catheters by nephrology trainees. *Ren Fail* 2013; **35**: 1264-1268 [PMID: 23924372 DOI: 10.3109/0886022X.2013.823875]

122 **Torreggiani M**, Scaramuzzi ML, Manini A, Castoldi F, Serpieri N, Maggi N, Sileno G, Migotto C, Esposito V, Montagna F, Esposito C. Hemodialysis vascular access: everything you always wanted to know about it (but were afraid to ask). *J Nephrol* 2013; **26**: 836-847 [PMID: 23023719 DOI: 10.5301/jn5000209]

123 **Ng PK**, Ault MJ, Maldonado LS. Peripherally inserted central catheters in the intensive care unit. *J Intensive Care Med* 1996; **11**: 49-54 [PMID: 10160070]

124 **Black IH**, Blosser SA, Murray WB. Central venous pressure measurements: peripherally inserted catheters versus centrally inserted catheters. *Crit Care Med* 2000; **28**: 3833-3836 [PMID: 11153622 DOI: 10.1097/00003246-200012000-00014]

125 **Galloway S**, Bodenham A. Long-term central venous access. *Br J Anaesth* 2004; **92**: 722-734 [PMID: 15003979 DOI: 10.1093/bja/aeh109]

126 **Pittiruti M**, Scoppettuolo G, Emoli A, Dolcetti L, Migliorini I, LaGreca A, Malerba M. Parenteral nutrition through ultrasound-placed PICCs and midline catheters is associated with a low rate of complications: an observational study. *Nutr Ther Metab* 2009; **27**: 142-148 [DOI: 10.5301/NTM.2012.9604]

127 **Di Giacomo M**. Comparison of three peripherally-inserted central catheters: pilot study. *Br J Nurs* 2009; **18**: 8-16 [PMID: 19127226]

128 **Bonizzoli M**, Batacchi S, Cianchi G, Zagli G, Lapi F, Tucci V, Martini G, Di Valvasone S, Peris A. Peripherally inserted central venous catheters and central venous catheters related thrombosis in post-critical patients. *Intensive Care Med* 2011; **37**: 284-289 [PMID: 20857280 DOI: 10.1007/s00134-010-2043-x]

129 **Trerotola SO**, Stavropoulos SW, Mondschein JI, Patel AA, Fishman N, Fuchs B, Kolansky DM, Kasner S, Pryor J, Chittams J. Triple-lumen peripherally inserted central catheter in patients in the critical care unit: prospective evaluation. *Radiology* 2010; **256**: 312-320 [PMID: 20574104 DOI: 10.1148/radiol.10091860]

130 **Nichols I**, Humphrey JP. The efficacy of upper arm placement of peripherally inserted central catheters using bedside ultrasound and microintroducer technique. *J Infus Nurs* 2008; **31**: 165-176 [PMID: 18496061 DOI: 10.1097/01.NAN.0000317703.66395.b8]

131 **Chopra V**, Anand S, Hickner A, Buist M, Rogers MA, Saint S, Flanders SA. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet* 2013; **382**: 311-325 [PMID: 23697825 DOI: 10.1016/S0140-6736(13)60592-9]

132 **Harnage SA**. Achieving zero catheter related blood stream infections: 15 months success in a community based medical center. *JAVA* 2007; **12**: 218-224 [DOI: 10.2309/java.12-4-8]

133 **Garnacho-Montero J**, Aldabó-Pallás T, Palomar-Martínez M, Vallés J, Almirante B, Garcés R, Grill F, Pujol M, Arenas-Giménez C, Mesalles E, Escoresca-Ortega A, de Cueto M, Ortiz-Leyba C. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. *Intensive Care Med* 2008; **34**: 2185-2193 [PMID: 18622596 DOI: 10.1007/s00134-008-1204-7]

134 **Fearonce G**, Faraklas I, Saffle JR, Cochran A. Peripherally inserted central venous catheters and central venous catheters in burn patients: a comparative review. *J Burn Care Res* 2010; **31**: 31-35 [PMID: 20061834 DOI: 10.1097/BCR.0b013e3181cb8eaa]

135 **Safdar N**, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. *Chest* 2005; **128**: 489-495 [PMID: 16100130]

P- Reviewer: Esposito C, Fulop T, Gow KW **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v3.i4.95

World J Crit Care Med 2014 November 4; 3(4): 95-101
ISSN 2220-3141 (online)

REVIEW

Impact of perioperative hyponatremia in children: A narrative review

Cheme Andersen, Arash Afshari

Cheme Andersen, Arash Afshari, Department of Anaesthesiology, Juliane Marie Centre, Rigshospitalet, 2100 Copenhagen, Denmark
Author contributions: Andersen C and Afshari A contributed to this paper.
Correspondence to: Cheme Andersen, MD, Department of Anaesthesiology, Juliane Marie Centre, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. chemeandersen@gmail.com
Telephone: +45-20680481
Received: July 19, 2014 Revised: September 13, 2014
Accepted: October 23, 2014
Published online: November 4, 2014

Abstract

For more than 50 years, hypotonic fluids (crystalloids) have been the standard for maintenance fluid used in children. In the last decade, several studies have evaluated the risk of hyponatremia associated with the use of hypotonic *vs* isotonic fluids, which has lead to an intense debate. Children undergoing surgery have several stimuli for release of antidiuretic hormone, which controls renal water handling, including pain, nausea, vomiting, narcotic use and blood loss. The body's primary defense against the development of hyponatremia is the ability of the kidneys to excrete free water and dilute urine. Increased levels of antidiuretic hormone can result in hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. This manifests as central nervous system symptoms such as lethargy, irritability and seizures. The risk for symptomatic hyponatremia is higher in children than in adults. It represents an emergency condition, and early diagnosis, prompt treatment and close monitoring are essential to reduce morbidity and mortality. The widespread use of hypotonic fluids in children undergoing surgery is a matter of concern and more focus on this topic is urgently needed. In this paper, we review the literature and describe the impact of perioperative hyponatremia in children.

Key words: Children; Fluid; Hyponatremia; Pediatric; Perioperative

Core tip: Hospital-acquired hyponatremia is common, particularly among children undergoing surgery. These children tend to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and they have a poorer prognosis. As the risk is increased by the use of hypotonic fluids, intraoperative fluids for children should be isotonic. Symptomatic hyponatremia should be corrected with 3% sodium chloride and close monitoring of the patient and serum sodium level is mandatory to prevent brain herniation and neurologic damage from cerebral ischemia.

Andersen C, Afshari A. Impact of perioperative hyponatremia in children: A narrative review. *World J Crit Care Med* 2014; 3(4): 95-101 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i4/95.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i4.95

INTRODUCTION

The overall goal of perioperative fluid management is to ensure adequate perfusion of tissue by administering maintenance fluids including electrolytes and glucose to replace preoperative fluid deficits and ongoing losses. Preoperative fluid status in children is affected by various factors, and a deficit is often due to prolonged fasting, dehydration (from diarrhea, vomiting and fever), bleeding and increased levels of stress. Inadequate fluid management may cause reduced cardiac output and oxygen delivery to damaged tissue, which is associated with an increased rate of postoperative complications[1]. On the other hand, overhydration can have equally severe consequences, such as acidosis, coagulation deficits and periph-

Table 1 The 4-2-1 formula for maintenance fluids in children[10,11]

Weight	Daily fluid requirements	Hourly fluid requirements
3-10 kg	100 mL/kg	4 mL/kg per hour
11-20 kg	1000 mL + 50 mL for every kilogram > 10	40 mL/h + 2 mL/h for every kilogram > 10
> 20 kg	1500 mL + 20 mL for every kilogram > 20	60 mL/h + 1 mL/h for every kilogram > 20

eral and pulmonary edema[2-5].

Children undergoing surgery are at a higher risk for developing hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. Accumulating evidence indicates that among those with a serum sodium < 125 mmol/L, more than 50% develop hyponatremic encephalopathy and are at a risk for seizure, respiratory failure and ultimately death[6-9]. Thus, correct perioperative fluid management is essential to avoid perioperative hyponatremia. This review discusses the recent evidence concerning this important and often neglected clinical condition in children.

MAINTENANCE FLUID IN CHILDREN

The calculation of maintenance fluid in children is based on Holliday and Segar's recommendations from 1957[10]. They described the physiologic deficits that result from fluid lost from the skin, respiratory tract, and urine, equivalent to approximately 100 mL/100 kcal metabolized per day. Their calculations have since evolved into the widely used "4-2-1 rule" (Table 1)[11,12]. However, this formula provides only for water maintenance, and does not consider correction of deficits or replacement of continuous, abnormal water loss. In 1975, Furman *et al*[13] suggested calculating the preoperative deficits by multiplying the hourly rate by the number of hours the patient was *nil per os*. Furthermore, they proposed replacing half of this deficit during the first hour of surgery, followed by administration of the other half over the next two hours. This method was simplified in 1986 by Berry[14] who proposed delivering a bolus of a 0.9% normal saline solution to otherwise healthy children over the first hour of surgery. Berry concluded that children three years of age and younger should receive 25 mL/kg, whereas children four years and older should receive 15 mL/kg. These methods were based on the assumption that the patients had been under *nil per os* for at least 6-8 h, though recent liberalization of fasting requirements may have decreased preoperative water loss[15-17].

PERIOPERATIVE HYPONATREMIA IN CHILDREN

Hyponatremia is the most common electrolyte abnormality found in hospitalized children[18,19]. The body's primary mechanism to prevent hyponatremia is the generation of dilute urine and excretion of free water by the kidneys. Renal water handling is generally controlled *via* antidiuretic hormone[20], the release of which is stimulated by pain, nausea, vomiting, narcotic use and blood loss, among others (Table 2), which are experienced by many children undergoing surgery[21,22]. Antidiuretic hormone can promote hyponatremia by increasing the permeability of collecting duct cells in the kidney, leading to the retention of free water. Subsequent influx of water into the brain *via* glial cell swelling can lead to cerebral edema, brain stem herniation and death[23-33].

Pediatric patients are more prone to symptomatic hyponatremia[34-38], which is mainly manifested as central nervous system symptoms, including lethargy, irritability, muscle weakness, seizures and coma or even death, in the most severe cases[39-42]. Furthermore, children undergoing surgery are also more likely to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults, with an estimated mortality of 8%[6]. Symptoms of hyponatremic encephalopathy are often unspecific and may appear as headache, nausea, vomiting and fatigue, which can easily be mistaken for normal symptoms after surgery and general anesthesia[24,43-47], but can rapidly progress to seizures, respiratory arrest and ultimately death or a permanent vegetative state as a complication of severe cerebral edema[48]. The associated poorer prognosis is probably due to a combination of physical and physiologic differences between adults and children[49,50]. Children have a higher brain:skull size ratio, as their brains reach adult size by six years of age, which is ten years before their skulls attain their final dimensions. One should keep in mind that in older adults, there is a progressive loss of brain volume whilst the volume inside the skull remains constant.

Critically ill children, and those in need of postoperative admission to intensive care units, are particularly at an increased risk for hyponatremia[51-57]. Hyponatremia in these children can be caused by normo- or hypervolemic conditions caused by heart failure, such as iatrogenic-induced hyponatremia (secondary to excessive water and/or salt insufficiency), renal insufficiency or a syndrome of inappropriate antidiuretic hormone secretion[58], or by hypovolemia from extra-renal volume loss (gastric, diarrhea, burn wounds, interstitial leakage), renal loss (polyuria after acute kidney failure, adrenocortical insufficiency) or excessive use of diuretics. Children with neurologic diseases, younger children with intracranial neoplasms, and those with hydrocephalus are also more prone to hyponatremia, which can be more complicated[59-67]. In a recent study, hyponatremic children with intracranial neoplasms had a five-fold increased risk of moderate or severe disability based on their Pediatric Cerebral Performance Category score at discharge, with hyponatremia independently associated with worse neurologic outcome despite adjustment for age and tumor factors[68]. The same group also found an increased risk of postoperative hyponatremia after neurosurgery among children that was independent of the preoperative degree of hyponatremia[69].

Table 2 Stimuli associated with increased antidiuretic hormone production (adapted from Bailey *et al*[15])

Hemodynamic	
Hypotension	
Hypovolemia	Blood loss, diarrhea, diuretics, vomiting, renal salt wasting, hypoaldosteronism, burns, polyuria
Hypervolemia	Nephrotic syndrome, cirrhosis, heart failure, hypoalbuminemia, iatrogenic-induced hyponatremia, excessive water intake
Non-hemodynamic	
Central nervous system disturbances	Meningitis, encephalitis, brain abscess, head injury, hypoxic brain injury, stroke
Pulmonary diseases	Asthma, pneumonia, chronic obstructive pulmonary disease, tuberculosis, empyema, bronchiolitis, acute respiratory failure
Cancer	Lung cancer (especially small-cell lung cancer), brain tumor, leukemia, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, neuroendocrine tumor, squamous cell carcinoma
Medications	Selective serotonin reuptake inhibitors, morphine, carbamazepine, cyclophosphamide, vincristine, desmopressin
Other	Pain, stress, nausea, emesis, postoperative state, cortisol deficiency

Table 3 Most commonly available crystalloid and human albumin solutions in Europe

Fluid	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	Lactate (mmol/L)	Acetate (mmol/L)	Glucose monohydrate (g/L)	Osmolarity (mOsm/L)	Tonicity (to plasma)
Isotonic NaCl	154	0	154	0	0	0	308 (iso-osmolar)	Isotonic
Ringer's lactate	130	4	109	28	0	0	270 (iso-osmolar)	Isotonic
Ringer's acetate	130	4	110	0	30	0	270 (iso-osmolar)	Isotonic
Darrow-glucose "SAD"	31	9	26	14	0	55	360 (hyperosmolar)	Hypotonic
Human albumin 5%	130-160	< 3	0	0	0	0	330 (hyperosmolar)	Isotonic
Human albumin 20%	100-160	< 3	0	0	0	0	300 (hyperosmolar)	Hypertonic
Glucosalin 2:1 (Glucose 3.3%/NaCl 0.3%)	51	0	51	0	0	33	287 (iso-osmolar)	Hypotonic
Glucose 2.5%/NaCl 0.45%	77	0	77	0	0	25	293 (iso-osmolar)	Hypotonic
Glucose 4%/NaCl 0.18%	31	0	31	0	0	40	284 (iso-osmolar)	Hypotonic
Glucose 5%/NaCl 0.45%	77	0	77	0	0	50	432 (hyperosmolar)	Hypotonic
Glucose 4.6%/NaCl 0.9%	154	0	154	0	0	46	561 (hyperosmolar)	Isotonic
Glucose 9.1%/NaCl 0.9%	154	0	154	0	0	91	813 (hyperosmolar)	Isotonic
Glucolyte (Glucose 5%/NaCl 0.3%/KCl 0.15%)	51	20	71	0	0	50	420 (hyperosmolar)	Hypotonic

However, there was a greater variation in serum sodium levels among the children with the most severe preoperative hyponatremia. Additionally, obstructive hydrocephalus and < 3.5 years of age were identified as significant independent risk factors for severe hyponatremia among those affected.

The risk for hospital-acquired hyponatremia and hyponatremic encephalopathy have been related to the use of hypotonic intravenous solutions[6,70-77]. Wang *et al*[78] found a significantly higher risk for hyponatremia and severe hyponatremia among pediatric patients administered hypotonic solutions compared with isotonic fluids in a systematic review of ten randomized clinical trials involving 855 subjects. Hyponatremia is also a concern in neonates, as intravenous hypotonic and free water intake of more than 6.5 mL/kg per hour during surgery reduces the number of postoperative plasma sodium measurements > 4 mmol/L[79,80]. Additionally, there was an adverse association between large (8-13 mmol/L) and very large (> 13 mmol/L) changes in serum sodium levels in the first few weeks of life and the risk of impaired functional outcomes at two years of age, with neuromotor impairments in particular.

CORRECTION OF HYPONATREMIA

To prevent brain herniation and neurologic damage from cerebral ischemia, cases of symptomatic hyponatremia require urgent correction of sodium levels to 4-6 mmol/L with 3% sodium chloride[48,81-86]. The rate of correction does not need to be restricted in patients with true acute hyponatremia, and modulation of excessive corrections is not indicated[87]. However, limits for correction are warranted if there is any uncertainty as to whether the hyponatremia is chronic or acute. It should be noted that correction of hypokalemia will also contribute to an increase in the serum sodium concentration. In the absence of severe or moderately severe symptoms, there is often sufficient time for diagnostic assessment and cause-specific treatment. Although children with severe hyponatremia need urgent, frequent and prolonged monitoring because of the risk of repeated sodium changes[69], correction with hypertonic saline is not indicated in asymptomatic cases[88,89].

CONCLUSION

As the use of hypotonic fluids is related to a higher risk of hyponatremia compared with isotonic fluids[90-93], it is difficult to justify their widespread use as a standard maintenance fluid in children during surgery. An ideal intraoperative fluid should have a tonicity and sodium concentration close to the physiologic range[94]. To avoid lipolysis, hypoglycemia, or hyperglycemia, 1.0%-2.5% glucose (rather than 5%) should be used and should also include metabolic anions (*i.e.*, acetate, lactate or malate) as bicarbonate precursors to prevent hyperchloremic acidosis. Most children need 2-3 mEq/kg per 24 h of sodium chloride, and the target serum sodium is between 135-140 mmol/L.

Monitoring of serum sodium levels in patients maintained by fluid infusion is critical, and certainly in children undergoing surgery as they are more vulnerable to hyponatremia than adults. Indeed, close monitoring is mandatory in symptomatic cases of hyponatremia, as they can rapidly progress to hyponatremic encephalopathy[95-100]. This complex problem remains an ongoing clinical challenge and deserves more attention by clinicians, not only in an academic context, but in clinical settings where there is ample evidence to support fluid therapy strategies that can reduce the risk of serious consequences for children. Additionally, the medical industry and researchers should increase their efforts to develop more appropriate and balanced intravenous solutions for children of various ages and conditions, due to the diverse availability of solutions across geographical regions (Table 3).

REFERENCES

1 **Pearse RM**, Ackland GL. Perioperative fluid therapy. *BMJ* 2012; **344**: e2865 [PMID: 22539015 DOI: 10.1136/bmj.e2865]
2 **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]
3 **Rosenberg AL**, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009; **24**: 35-46 [PMID: 19103612 DOI: 10.1177/0885066608329850]
4 **Chappell D**, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723-740 [PMID: 18813052 DOI: 10.1097/ALN.0b013e3181863117]
5 **Silva JM**, de Oliveira AM, Nogueira FA, Vianna PM, Pereira Filho MC, Dias LF, Maia VP, Neucamp Cde S, Amendola CP, Carmona MJ, Malbouisson LM. The effect of excess fluid balance on the mortality rate of surgical patients: a multicenter prospective study. *Crit Care* 2013; **17**: R288 [PMID: 24326085]
6 **Moritz ML**, Ayus JC. Preventing neurological complications from dysnatremias in children. *Pediatr Nephrol* 2005; **20**: 1687-1700 [PMID: 16079988 DOI: 10.1007/s00467-005-1933-6]
7 **Eulmesekian PG**, Pérez A, Minces PG, Bohn D. Hospital-acquired hyponatremia in postoperative pediatric patients: prospective observational study. *Pediatr Crit Care Med* 2010; **11**: 479-483 [PMID: 20124948 DOI: 10.1097/PCC.0b013e3181ce7154]
8 **Dearlove OR**, Ram AD, Natsagdoy S, Humphrey G, Cunliffe M, Potter F. Hyponatraemia after postoperative fluid management in children. *Br J Anaesth* 2006; **97**: 897-898; author reply 898 [PMID: 17098726 DOI: 10.1093/bja/ael298]
9 **Au AK**, Ray PE, McBryde KD, Newman KD, Weinstein SL, Bell MJ. Incidence of postoperative hyponatremia and complications in critically-ill children treated with hypotonic and normotonic solutions. *J Pediatr* 2008; **152**: 33-38 [PMID: 18154895 DOI: 10.1016/j.jpeds.2007.08.040]
10 **Holliday MA**, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957; **19**: 823-832 [PMID: 13431307 DOI: 10.1097/01.aco.0000192818.68730.9d]
11 **Paut O**, Lacroix F. Recent developments in the perioperative fluid management for the paediatric patient. *Curr Opin Anaesthesiol* 2006; **19**: 268-277 [PMID: 16735810]
12 **Murat I**, Dubois MC. Perioperative fluid therapy in pediatrics. *Paediatr Anaesth* 2008; **18**: 363-370 [PMID: 18312509 DOI: 10.1111/j.1460-9592.2008.02505.x]
13 **Furman EB**, Roman DG, Lemmer LA, Hairabet J, Jasinska M, Laver MB. Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. *Anesthesiology* 1975; **42**: 187-193 [PMID: 1115368]
14 **Berry F**. Practical aspects of fluid and electrolyte therapy. In: Berry F, editor. Anesthetic Management of Difficult and Routine Pediatric Patients. New York: Churchill Livingstone, 1986: 107-135
15 **Bailey AG**, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? *Anesth Analg* 2010; **110**: 375-390 [PMID: 19955503 DOI: 10.1213/ANE.0b013e3181b6b3b5]
16 **Smith I**, Kranke P, Murat I, Smith A, O'Sullivan G, Søreide E, Spies C, in't Veld B. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011; **28**: 556-569 [PMID: 21712716 DOI: 10.1097/EJA.0b013e3283495ba1]
17 **Arun BG**, Korula G. Preoperative fasting in children: An audit and its implications in a tertiary care hospital. *J Anaesthesiol Clin Pharmacol* 2013; **29**: 88-91 [PMID: 23493776 DOI: 10.4103/0970-9185.105810]
18 **Cavari Y**, Pitfield AF, Kissoon N. Intravenous maintenance fluids revisited. *Pediatr Emerg Care* 2013; **29**: 1225-1228; quiz 1229-1231 [PMID: 24196097 DOI: 10.1097/PEC.0b013e3182aa4e2a]
19 **Moritz ML**, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. *Pediatr Nephrol* 2010; **25**: 1225-1238 [PMID: 19894066 DOI: 10.1007/s00467-009-1323-6]
20 **Ghali JK**. Mechanisms, risks, and new treatment options for hyponatremia. *Cardiology* 2008; **111**: 147-157 [PMID: 18434717 DOI: 10.1159/000121596]
21 **Moritz ML**, Ayus JC. Hospital-acquired hyponatremia--why are hypotonic parenteral fluids still being used? *Nat Clin Pract Nephrol* 2007; **3**: 374-382 [PMID: 17592470]
22 **Carcillo JA**. Intravenous fluid choices in critically ill children. *Curr Opin Crit Care* 2014; **20**: 396-401 [PMID: 24979714 DOI: 10.1097/MCC.0000000000000119]
23 **Ayus JC**, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. *Am J Physiol Renal Physiol* 2008; **295**: F619-F624 [PMID: 18448591 DOI: 10.1152/ajprenal.00502.2007]
24 **Grissinger M**. Hyponatremia and death in Healthy children From plain dextrose and Hypotonic Saline Solutions after Surgery. *P T* 2013; **38**: 364-388 [PMID: 24049421]
25 **Fraser CL**, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. *Am J Med* 1997; **102**: 67-77 [PMID: 9209203 DOI: 10.1016/S0002-9343(96)00274-4]
26 **Ayus JC**, Arieff AI. Pathogenesis and prevention of hyponatremic encephalopathy. *Endocrinol Metab Clin North Am* 1993; **22**: 425-446 [PMID: 8325296]
27 **Moritz ML**, Ayus JC. Prevention of hospital-acquired hypo-

natremia: a case for using isotonic saline. *Pediatrics* 2003; **111**: 227-230 [PMID: 12563043 DOI: 10.1542/peds.111.2.227]
28 **Achinger SG**, Moritz ML, Ayus JC. Dysnatremias: why are patients still dying? *South Med J* 2006; **99**: 353-362; quiz 363-364 [PMID: 16634244]
29 **Sterns RH**, Hix JK, Silver SM. Management of hyponatremia in the ICU. *Chest* 2013; **144**: 672-679 [PMID: 23918113 DOI: 10.1378/chest.12-2600]
30 **Halawa I**, Andersson T, Tomson T. Hyponatremia and risk of seizures: a retrospective cross-sectional study. *Epilepsia* 2011; **52**: 410-413 [PMID: 21314679 DOI: 10.1111/j.1528-1167.2010.02939.x]
31 **Beck CE**, Choong K, Puligandla PS, Hartfield D, Holland J, Lacroix J, Friedman JN. Avoiding hypotonic solutions in paediatrics: Keeping our patients safe. *Paediatr Child Health* 2013; **18**: 94-95 [PMID: 24421665]
32 **Goh KP**. Management of hyponatremia. *Am Fam Physician* 2004; **69**: 2387-2394 [PMID: 15168958]
33 **Nathan BR**. Cerebral correlates of hyponatremia. *Neurocrit Care* 2007; **6**: 72-78 [PMID: 17356196]
34 **Davison D**, Basu RK, Goldstein SL, Chawla LS. Fluid management in adults and children: core curriculum 2014. *Am J Kidney Dis* 2014; **63**: 700-712 [PMID: 24332766 DOI: 10.1053/j.ajkd.2013.10.044]
35 **Choong K**, Arora S, Cheng J, Farrokhyar F, Reddy D, Thabane L, Walton JM. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. *Pediatrics* 2011; **128**: 857-866 [PMID: 22007013 DOI: 10.1542/peds.2011-0415]
36 **Easley D**, Tillman E. Hospital-acquired hyponatremia in pediatric patients: a review of the literature. *J Pediatr Pharmacol Ther* 2013; **18**: 105-111 [PMID: 23798904 DOI: 10.5863/1551-6776-18.2.105]
37 **Hardesty DA**, Kilbaugh TJ, Storm PB. Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients. *Neurocrit Care* 2012; **17**: 382-387 [PMID: 21822747 DOI: 10.1007/s12028-011-9618-4]
38 **Alves JT**, Troster EJ, Oliveira CA. Isotonic saline solution as maintenance intravenous fluid therapy to prevent acquired hyponatremia in hospitalized children. *J Pediatr* (Rio J) 2011; **87**: 478-486 [PMID: 22170285 DOI: 10.2223/JPED.2133]
39 **Adrogué HJ**, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581-1589 [PMID: 10824078 DOI: 10.1056/NEJM200005253422107]
40 **Koczmara C**, Wade AW, Skippen P, Campigotto MJ, Streitenberger K, Carr R, Wong E, Robertson K. Hospital-acquired acute hyponatremia and reports of pediatric deaths. *Dynamics* 2010; **21**: 21-26 [PMID: 20333891]
41 **Smith DM**, McKenna K, Thompson CJ. Hyponatraemia. *Clin Endocrinol* (Oxf) 2000; **52**: 667-678 [PMID: 10848869 DOI: 10.1046/j.1365-2265.2000.01027.x]
42 **Halberthal M**, Halperin ML, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ* 2001; **322**: 780-782 [PMID: 11282868]
43 **Moran D**, Fronk C, Mandel E. Managing hyponatremia in adults. *JAAPA* 2014; **27**: 23-29; quiz 30 [PMID: 24622398 DOI: 10.1097/01.JAA.0000444730.86174.e8]
44 **Keane M**. Recognising and managing acute hyponatraemia. *Emerg Nurse* 2014; **21**: 32-36; quiz 37 [PMID: 24494770 DOI: 10.7748/en2014.02.21.9.32.e1128]
45 **Reddy P**, Mooradian AD. Diagnosis and management of hyponatraemia in hospitalised patients. *Int J Clin Pract* 2009; **63**: 1494-1508 [PMID: 19769706 DOI: 10.1111/j.1742-1241.2009.02103.x]
46 **Koźniewska E**, Podlecka A, Rafałowska J. Hyponatremic encephalopathy--some experimental and clinical findings. *Folia Neuropathol* 2003; **41**: 41-45 [PMID: 12862395]
47 **Auroy Y**, Benhamou D, Péquignot F, Jougla E, Lienhart A. Hyponatraemia-related death after paediatric surgery still exists in France. *Br J Anaesth* 2008; **101**: 741 [PMID: 18854387 DOI: 10.1093/bja/aen282]
48 **Verbalis JG**, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; **126**: S1-42 [PMID: 24074529 DOI: 10.1016/j.amjmed.2013.07.006]
49 **Playfor SD**. Hypotonic intravenous solutions in children. *Expert Opin Drug Saf* 2004; **3**: 67-73 [PMID: 14680463 DOI: 10.1517/14740338.3.1.67]
50 **Arieff AI**, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992; **304**: 1218-1222 [PMID: 1515791 DOI: 10.1136/bmj.304.6836.1218]
51 **Luu R**, DeWitt PE, Reiter PD, Dobyns EL, Kaufman J. Hyponatremia in children with bronchiolitis admitted to the pediatric intensive care unit is associated with worse outcomes. *J Pediatr* 2013; **163**: 1652-1656.e1 [PMID: 23910686 DOI: 10.1016/j.jpeds.2013.06.041]
52 **Singhi S**, Jayashre M. Free water excess is not the main cause for hyponatremia in critically ill children receiving conventional maintenance fluids. *Indian Pediatr* 2009; **46**: 577-583 [PMID: 19430087]
53 **Choong K**, Bohn D. Maintenance parenteral fluids in the critically ill child. *J Pediatr* (Rio J) 2007; **83**: S3-S10 [PMID: 17486196 DOI: 10.1590/S0021-75572007000300002]
54 **Roberts KE**. Pediatric fluid and electrolyte balance: critical care case studies. *Crit Care Nurs Clin North Am* 2005; **17**: 361-373, x [PMID: 16344206 DOI: 10.1016/j.ccell.2005.07.006]
55 **Singhi S**. Hyponatremia in hospitalized critically ill children: current concepts. *Indian J Pediatr* 2004; **71**: 803-807 [PMID: 15448387 DOI: 10.1007/BF02730718]
56 **Moritz ML**, Ayus JC. Dysnatremias in the critical care setting. *Contrib Nephrol* 2004; **144**: 132-157 [PMID: 15264404 DOI: 10.1159/000078883]
57 **Stelfox HT**, Ahmed SB, Zygun D, Khandwala F, Laupland K. Characterization of intensive care unit acquired hyponatremia and hypernatremia following cardiac surgery. *Can J Anaesth* 2010; **57**: 650-658 [PMID: 20405264 DOI: 10.1007/s12630-010-9309-1]
58 **Peri A**, Giuliani C. Management of euvolemic hyponatremia attributed to SIADH in the hospital setting. *Minerva Endocrinol* 2014; **39**: 33-41 [PMID: 24513602]
59 **Al-Zahraa Omar F**, Al Bunyan M. Severe hyponatremia as poor prognostic factor in childhood neurologic diseases. *J Neurol Sci* 1997; **151**: 213-216 [PMID: 9349678]
60 **Williams C**, Simon TD, Riva-Cambrin J, Bratton SL. Hyponatremia with intracranial malignant tumor resection in children. *J Neurosurg Pediatr* 2012; **9**: 524-529 [PMID: 22546031 DOI: 10.3171/2012.1.PEDS11465]
61 **Hardesty DA**, Sanborn MR, Parker WE, Storm PB. Perioperative seizure incidence and risk factors in 223 pediatric brain tumor patients without prior seizures. *J Neurosurg Pediatr* 2011; **7**: 609-615 [PMID: 21631197 DOI: 10.3171/2011.3.PEDS1120]
62 **Lang SS**, Bauman JA, Aversano MW, Sanborn MR, Vossough A, Heuer GG, Storm PB. Hyponatremia following endoscopic third ventriculostomy: a report of 5 cases and analysis of risk factors. *J Neurosurg Pediatr* 2012; **10**: 39-43 [PMID: 22702328 DOI: 10.3171/2012.4.PEDS1222]
63 **Bettinelli A**, Longoni L, Tammaro F, Faré PB, Garzoni L, Bianchetti MG. Renal salt-wasting syndrome in children with intracranial disorders. *Pediatr Nephrol* 2012; **27**: 733-739 [PMID: 22237777 DOI: 10.1007/s00467-011-2093-5]
64 **Coenraad MJ**, Meinders AE, Taal JC, Bolk JH. Hyponatremia in intracranial disorders. *Neth J Med* 2001; **58**: 123-127 [PMID: 11246111]
65 **Soupart A**, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications.

Clin Nephrol 1996; **46**: 149-169 [PMID: 8879850]
66 **Betjes MG**. Hyponatremia in acute brain disease: the cerebral salt wasting syndrome. *Eur J Intern Med* 2002; **13**: 9-14 [PMID: 11836078 DOI: 10.1016/S0953-6205(01)00192-3]
67 **Tzamaloukas AH**, Malhotra D, Rosen BH, Raj DS, Murata GH, Shapiro JI. Principles of management of severe hyponatremia. *J Am Heart Assoc* 2013; **2**: e005199 [PMID: 23525443 DOI: 10.1161/JAHA.112.005199]
68 **Williams CN**, Belzer JS, Riva-Cambrin J, Presson AP, Bratton SL. The incidence of postoperative hyponatremia and associated neurological sequelae in children with intracranial neoplasms. *J Neurosurg Pediatr* 2014; **13**: 283-290 [PMID: 24410125 DOI: 10.3171/2013.12.PEDS13364]
69 **Belzer JS**, Williams CN, Riva-Cambrin J, Presson AP, Bratton SL. Timing, duration, and severity of hyponatremia following pediatric brain tumor surgery*. *Pediatr Crit Care Med* 2014; **15**: 456-463 [PMID: 24777301 DOI: 10.1097/PCC.0000000000000154]
70 **Pemde HK**, Dutta AK, Sodani R, Mishra K. Isotonic Intravenous Maintenance Fluid Reduces Hospital Acquired Hyponatremia in Young Children with Central Nervous System Infections. *Indian J Pediatr* 2014; Epub ahead of print [PMID: 24830423]
71 **Carandang F**, Anglemyer A, Longhurst CA, Krishnan G, Alexander SR, Kahana M, Sutherland SM. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr* 2013; **163**: 1646-1651 [PMID: 23998517 DOI: 10.1016/j.jpeds.2013.07.020]
72 **Foster BA**, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr* 2014; **165**: 163-169.e2 [PMID: 24582105 DOI: 10.1016/j.jpeds.2014.01.040]
73 **Yung M**, Keeley S. Randomised controlled trial of intravenous maintenance fluids. *J Paediatr Child Health* 2009; **45**: 9-14 [PMID: 18036144]
74 **Montañana PA**, Modesto i Alapont V, Ocón AP, López PO, López Prats JL, Toledo Parreño JD. The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. *Pediatr Crit Care Med* 2008; **9**: 589-597 [PMID: 18838929 DOI: 10.1097/PCC.0b013e31818d3192]
75 **Rey C**, Los-Arcos M, Hernández A, Sánchez A, Díaz JJ, López-Herce J. Hypotonic versus isotonic maintenance fluids in critically ill children: a multicenter prospective randomized study. *Acta Paediatr* 2011; **100**: 1138-1143 [PMID: 21352357 DOI: 10.1111/j.1651-2227.2011.02209.x]
76 **Hanna M**, Saberi MS. Incidence of hyponatremia in children with gastroenteritis treated with hypotonic intravenous fluids. *Pediatr Nephrol* 2010; **25**: 1471-1475 [PMID: 20108002 DOI: 10.1007/s00467-009-1428-y]
77 **Hoorn EJ**, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. *Pediatrics* 2004; **113**: 1279-1284 [PMID: 15121942]
78 **Wang J**, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics* 2014; **133**: 105-113 [PMID: 24379232 DOI: 10.1542/peds.2013-2041]
79 **Edjo Nkilly G**, Michelet D, Hilly J, Diallo T, Greff B, Mangalsuren N, Lira E, Bounadja I, Brasher C, Bonnard A, Malbezin S, Nivoche Y, Dahmani S. Postoperative decrease in plasma sodium concentration after infusion of hypotonic intravenous solutions in neonatal surgery. *Br J Anaesth* 2014; **112**: 540-545 [PMID: 24193323 DOI: 10.1093/bja/aet374]
80 **Baraton L**, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Rozé JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. *Pediatrics* 2009; **124**: e655-e661 [PMID: 19752079 DOI: 10.1542/peds.2008-3415]
81 **Moritz ML**, Ayus JC. Management of hyponatremia in various clinical situations. *Curr Treat Options Neurol* 2014; **16**: 310 [PMID: 25099180 DOI: 10.1007/s11940-014-0310-9]
82 **Sterns RH**, Hix JK, Silver S. Treatment of hyponatremia. *Curr Opin Nephrol Hypertens* 2010; **19**: 493-498 [PMID: 20539224 DOI: 10.1097/MNH.0b013e32833bfa64]
83 **Sarnaik AP**, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. *Crit Care Med* 1991; **19**: 758-762 [PMID: 2055051 DOI: 10.1097/00003246-199106000-00005]
84 **Youn KS**, Tokeshi J. Therapy with hypertonic saline in combination with anti-convulsants for hyponatremia-induced seizure: a case report and review of the literature. *Hawaii Med J* 2002; **61**: 280-281 [PMID: 12632826]
85 **Decaux G**, Soupart A. Treatment of symptomatic hyponatremia. *Am J Med Sci* 2003; **326**: 25-30 [PMID: 12861122 DOI: 10.1097/00000441-200307000-00004]
86 **Moritz ML**, Ayus JC. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. *Metab Brain Dis* 2010; **25**: 91-96 [PMID: 20221678 DOI: 10.1007/s11011-010-9173-2]
87 **Spasovski G**, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014; **29** Suppl 2: i1-i39 [PMID: 24569496 DOI: 10.1093/ndt/gfu040]
88 **Zieg J**. Evaluation and management of hyponatraemia in children. *Acta Paediatr* 2014; **103**: 1027-1034 [PMID: 24862500 DOI: 10.1111/apa.12705]
89 **Moritz ML**, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. *Nephrol Dial Transplant* 2003; **18**: 2486-2491 [PMID: 14605269]
90 **Freeman MA**, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. *Acta Paediatr* 2012; **101**: e465-e468 [PMID: 22765308 DOI: 10.1111/j.1651-2227.2012.02780.x]
91 **Way C**, Dhamrait R, Wade A, Walker I. Perioperative fluid therapy in children: a survey of current prescribing practice. *Br J Anaesth* 2006; **97**: 371-379 [PMID: 16873386]
92 **Lee JM**, Jung Y, Lee SE, Lee JH, Kim KH, Koo JW, Park YS, Cheong HI, Ha IS, Choi Y, Kang HG. Intravenous fluid prescription practices among pediatric residents in Korea. *Korean J Pediatr* 2013; **56**: 282-285 [PMID: 23908667 DOI: 10.3345/kjp.2013.56.7.282]
93 **Keijzers G**, McGrath M, Bell C. Survey of paediatric intravenous fluid prescription: are we safe in what we know and what we do? *Emerg Med Australas* 2012; **24**: 86-97 [PMID: 22313565 DOI: 10.1111/j.1742-6723.2011.01503.x]
94 **Sümpelmann R**, Becke K, Crean P, Jöhr M, Lönnqvist PA, Strauss JM, Veyckemans F. European consensus statement for intraoperative fluid therapy in children. *Eur J Anaesthesiol* 2011; **28**: 637-639 [PMID: 21654319 DOI: 10.1097/EJA.0b013e3283446bb8]
95 **Rosner MH**, Ronco C. Dysnatremias in the intensive care unit. *Contrib Nephrol* 2010; **165**: 292-298 [PMID: 20427980 DOI: 10.1159/000313769]
96 **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]
97 **Pokaharel M**, Block CA. Dysnatremia in the ICU. *Curr Opin Crit Care* 2011; **17**: 581-593 [PMID: 22027406 DOI: 10.1097/MCC.0b013e32834cd388]
98 **Schrier RW**, Bansal S. Diagnosis and management of hyponatremia in acute illness. *Curr Opin Crit Care* 2008; **14**: 627-634 [PMID: 19005303 DOI: 10.1097/MCC.0b013e32830e45e3]
99 **Siragy HM**. Hyponatremia, fluid-electrolyte disorders, and

the syndrome of inappropriate antidiuretic hormone secretion: diagnosis and treatment options. *Endocr Pract* 2006; **12**: 446-457 [PMID: 16901803 DOI: 10.4158/EP.12.4.446]

100 **Sedlacek M**, Schoolwerth AC, Remillard BD. Electrolyte disturbances in the intensive care unit. *Semin Dial* 2006; **19**: 496-501 [PMID: 17150050 DOI: 10.1111/j.1525-139X.2006.00212.x]

P- Reviewer: Sterns RH, Tzamaloukas A
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v3.i4.102

World J Crit Care Med 2014 November 4; 3(4): 102-112
ISSN 2220-3141 (online)

REVIEW

Invasive candidiasis in critical care setting, updated recommendations from "Invasive Fungal Infections-Clinical Forum", Iran

Ashraf Elhoufi, Arezoo Ahmadi, Amir Mohammad Hashem Asnaashari, Mohammad Ali Davarpanah, Behrooz Farzanegan Bidgoli, Omid Moradi Moghaddam, Mohammad Torabi-Nami, Saeed Abbasi, Malak El-Sobky, Ali Ghaziani, Mohammad Hossein Jarrahzadeh, Reza Shahrami, Farzad Shirazian, Farhad Soltani, Homeira Yazdinejad, Farid Zand

Ashraf Elhoufi, Department of Critical Care Medicine, Dubai Hospital, Dubai Health Authority, Dubai 7272, United Arab Emirates
Arezoo Ahmadi, Department of Anesthesiology and Critical Care, Sina Hospital, Tehran University of Medical Sciences, Tehran 1136746911, Iran
Amir Mohammad Hashem Asnaashari, Department of Pulmonology and Critical Care, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad 45191735, Iran
Mohammad Ali Davarpanah, Department of Infectious Diseases and Tropical Medicine, Shiraz University of Medical Sciences, Shiraz 7134814336, Iran
Behrooz Farzanegan Bidgoli, Tracheal Disease Research Center, Shahid Behesti University of Medical Sciences, Tehran 1956944413, Iran
Omid Moradi Moghaddam, Department of Anesthesiology and Critical Care, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran 145151366, Iran
Mohammad Torabi-Nami, Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz 7134814336, Iran
Mohammad Torabi-Nami, Behphar Scientific Committee, Behphar Group, Tehran 1991915613 Iran
Saeed Abbasi, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan 7346181746, Iran
Malak El-Sobky, Invasive Fungal Infections-Clinical Forum, Dubai 9662 United Arab Emirates
Ali Ghaziani, Intensive Care and Burn Units, Motahhari Hospital, Tehran 1996714353, Iran
Mohammad Hossein Jarrahzadeh, Reza Shahrami, Invasive Fungal Infections-Clinical Forum, Tehran 1991915613 Iran
Farzad Shirazian, Intensive Care Unit, Vali-e-Asr Hospital, NAJA University, Tehran 19967, Iran
Farhad Soltani, Department of Anesthesiology and Critical Care, Golestan Hospital, Ahwaz Jundishapur University of Medical Sciences, Ahwaz 6135715794, Iran
Homeira Yazdinejad, Department of Anesthesiology and Critical Care, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran 1985717443, Iran
Farid Zand, Shiraz Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz 7134814336, Iran
Author contributions: Elhoufi A moderated the clinical forum and contributed to literature review; other than the first author, at second order, Ahmadi A, Asnaashari AMH, Davarpanah MA, Farzanegan Bidgoli B, Moradi Moghaddam O and Torabi-Nami M equally contributed to literature review and plenary talks as well as summary of recommendations (sorted alphabetically as second-order authors); at third order, Abbasi S, El-Sobky M, Ghaziani A, Jarrahzadeh MH, Shahrami R, Shirazian F, Soltani F, Yazdinejad H and Zand F equally contributed to this consensus through inputs and critical reversion of the manuscript for important intellectual content (sorted alphabetically as third-order authors); Torabi-Nami M drafted the manuscript; Torabi-Nami M and El-Sobky M provided technical material support; all authors read and approved the final manuscript.
Correspondence to: Mohammad Torabi-Nami, MD, PhD, Assistant Professor of Neuroscience, Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Zand St., Shiraz 7134814336, Iran. torabinami@sums.ac.ir
Telephone: +98-713-2317523 Fax: +98-713-2318042
Received: August 31, 2014 Revised: September 24, 2014
Accepted: October 23, 2014
Published online: November 4, 2014

Abstract

Invasive candidiasis (IC) bears a high risk of morbidity and mortality in the intensive care units (ICU). With the current advances in critical care and the use of wide-spectrum antibiotics, invasive fungal infections (IFIs) and IC in particular, have turned into a growing concern in the ICU. Further to blood cultures, some auxil-

iary laboratory tests and biomarkers are developed to enable an earlier detection of infection, however these test are neither consistently available nor validated in our setting. On the other hand, patients' clinical status and local epidemiology data may justify the empiric antifungal approach using the proper antifungal option. The clinical approach to the management of IC in febrile, non-neutropenic critically ill patients has been defined in available international guidelines; nevertheless such recommendations need to be customized when applied to our local practice. Over the past three years, Iranian experts from intensive care and infectious diseases disciplines have tried to draw a consensus on the management of IFI with a particular focus on IC in the ICU. The established IFI-clinical forum (IFI-CF), comprising the scientific leaders in the field, has recently come up with and updated recommendation on the same (June 2014). The purpose of this review is to put together literature insights and Iranian experts' opinion at the IFI-CF, to propose an updated practical overview on recommended approaches for the management of IC in the ICU.

Key words: Invasive candidiasis; Intensive care unit; IFI-clinical forum; Recommendations; Iran

Core tip: The present consensus statement has attempted to summarize the practical highlights regarding the management of Invasive Candidiasis (IC) in critical care setting. This easy-to-follow clinical pathway is expected to be not only of interest but also of clinical use for those who deal with the management of invasive fungal infections in hospital setting and especially the intensive care units. The focus of this paper is the concept of timely management of IC in critically ill patients.

Elhoufi A, Ahmadi A, Asnaashari AMH, Davarpanah MA, Farzanegan Bidgoli B, Moradi Moghaddam O, Torabi-Nami M, Abbasi S, El-Sobky M, Ghaziani A, Jarrahzadeh MH, Shahrami R, Shirazian F, Soltani F, Yazdinejad H, Zand F. Invasive candidiasis in critical care setting, updated recommendations from "Invasive Fungal Infections-Clinical Forum", Iran. *World J Crit Care Med* 2014; 3(4): 102-112 Available from: URL: http://www.wjgnet.com/2220-3141/full/v3/i4/102.htm DOI: http://dx.doi.org/10.5492/wjccm.v3.i4.102

INTRODUCTION

Despite the remarkable progress in the diagnostic and therapeutic approaches, infections continue to be a critical challenge in the intensive care units (ICUs) worldwide[1]. The use of wide-spectrum antibiotics, advanced care in the ICU and improved knowledge on fungal infections have potentially led to an increased incidence of invasive fungal infections (IFIs) especially in critically ill and immunosuppressed patients[2-4]. IFIs are shown to be often hard to diagnose and treat in critical care setting[4]. Timely management of IFIs based on risk stratification and empirical approach is shown to be of meaningful clinical benefit, meanwhile dependence on the culture results and relying on fungal biomarkers may delay clinical decisions and lead to potential complications, morbidity and mortality in such patients[5,6]. There are risk prediction models which suggest empirical approach for patients who are supposed to significantly benefit from empirical antifungal therapy[7,8]. Despite the validated clinical impact of applying IFIs' predictive tools such as Candida Score[9,10], many clinicians seem not to be consistently using them in routine practice[11]. This report is based on the communicated insights and position statements within the IFI-clinical forum comprising an Iranian panel of intensive care experts. The present article summarizes a literature review on the role of IFIs in mortality and morbidity in critical care setting, experts' panel inputs as well as updates on the local consensus and international guidelines with regard to the management of invasive candidiasis (IC) in ICU patients.

THE UNMET NEED WHICH PROMPTED AN "IFI-CLINICAL FORUM" ESTABLISHMENT

In compliance with the international guidelines on the management of IC in ICU, a group of Iranian experts in the fields of intensive care and infectious disease consolidated a consensus as a simple algorithmic approach in the management of IC in critical care setting in 2013[12]. This was primarily rooting in an earlier local consensus on the same, published in 2011; while the first report was predominantly based upon the infectious disease experts' opinion[13]. Pursuant to the above publications, an IFI-Clinical Forum (IFI-CF) comprising Iranian critical care experts and infectious disease specialists was established in 2014. The IFI-CF was formed to pursue clinical research, idea exchange and regular updates and recommendations with regard to optimal management of IFIs. The forum attempts to improve the current situation in the diagnosis and management of IC in critical care units by means of continued education, research and promoting evidence-based practice.

To reach the above, field experts from different universities across Iran attended a round table discussion on 26-27 June 2014. Discussions in this clinical forum revolved around updated epidemiologic insights on IC in ICU, the related diagnostic challenges, therapeutic approaches and proper antifungal options in ICU-admitted patients afflicted with IC.

The meeting objectives, established as part of the planning process, were used to guide development of meeting content and activities. Following two days of scientific debates, reviewing evidence and case discussions, the panel could unanimously draw an updated recommendation for the management of IC in the ICU. This meeting and similar future ones will hopefully allow opti-

mizing models of patient care with regard to IFIs in ICU through an inter-professional influence.

Materializing the above perspective is believed to depend upon five tenets including: 1-classifying the critically ill patients' risk for IFIs, 2-defining a timely and reasonable approach for treating IFIs in ICU-admitted patients, 3-developing center-based algorithms for diagnosis, treatment and surveillance of ICU patients with high risk of IFIs, as epidemiology may differ center by center, 4-determining advantages and disadvantages of antifungal options when used in the ICU and 5-optimizing antifungal treatment paradigm in our local setting for ICU patients who are at increased risk or clinical suspicion for IFIs.

LITERATURE REVIEW, PARTICIPANTS AND GROUP CONSENSUS

A systematic literature search in PubMed, Scopus, Cochrane and Google Scholar databases (1990-2014) was conducted using the combination of our keywords including invasive fungal infections, ICU, diagnosis, treatment approach, antifungal therapy and recommendations. Following the cross-check, documents describing the significance of IFIs in ICU and recommendations for diagnosis and treatment approaches were isolated for review and discussions. Most recent guidelines[12,14-17] and relevant papers were circulated among all IFI-CF attendees one month prior to the meeting.

The IFI-CF delegates discussed the available evidence, shortcomings and clinical challenges in the management of IFIs and particularly IC in ICU-admitted patients. Each delegate was invited based on his/her expertise in the management of IC and other fungal infections in critical care setting. All experts actively participated during the plenary talks, problem-based round table discussions and case studies over a 2-d interactive discussion forum. Through a point-to-point systematic approach and discussions on key issues such as: 1-local epidemiology of IFIs, 2-preferred diagnostic and therapeutic approaches, 3-implication of risk prediction tools and 4-optimized antifungal therapy, the available evidence as well as participants' inputs/responses were compiled to draw a clinical pathway.

EPIDEMIOLOGIC INSIGHTS ON INVASIVE CANDIDIASIS; A GLOBAL AND LOCAL PROBLEM ON THE RISE

The current advances in critical care and the advent of broad-spectrum antibiotics not only have resulted in patients' longer survival but also in increasing the incidence of opportunistic infections such as IFIs over the past decade[18]. Currently, IFIs constitute a clinical issue on the rise in the ICUs both in the developing and developed world[19,20]. Predisposing factors such as patients' complicated medical or surgical status, invasive bedside procedure and wide administration of antibiotics have contributed to increased rate of IFIs, mainly IC and invasive aspergillosis (IA), in the ICU[21-23]. *Candidemia* is thus far known to be the most prevalent fungal infection afflicting ICU patients[23]. According to an elegant survey which was carried out in over 1000 ICUs in more than 70 countries, almost one fifth of the isolated pathogens in ICU patients were found to be fungi[24]. Based on the same report, *Candida* species (spp.) were almost 10 times more isolated than aspergillosis and known to be linked with a high mortality and increased hospital length of stay (LoS) as well as medical care cost[24]. Since most of the diagnostic tests lack proper specificity and the culture result normally requires a long time, diagnosis of IFIs and IC in particular remains a challenge. Cumulating evidence suggest that institution of appropriate antifungal therapy upon initial clinical suspicion of IFIs is crucial for a positive outcome[8].

The increasing risk of IFIs in ICU, as well as the criticality of the timely decision making on treatment with the most proper options, have turned IFIs' management to a difficult task for intensivists. While the incidence of IFIs in immunocompromised hosts such as transplanted patients, those with hematologic malignancies or human immunodeficiency virus is significant, this report focuses on IFIs in non-neutropenic critically ill ICU-admitted patients. *Candida* spp. are considered the fourth most common blood stream infection (BSI) isolated from ICU-admitted patients in the West[25]. Where *Candida albicans* (*C. albicans*) has long been regarded as the most prevalent candida type, the relatively recent emergence of non-albicans species such as fluconazole-resistant *Candida krusei* (*C. krusei*) and *Candida glabrata* (*C. glabrata*) has turned into a challenge[20,25]. Recent data suggests an increased incidence of non-albicans *Candida* species. As such, *C. glabrata* and *Candida parapsilosis* (*C. parapsilosis*) are now ranked as second in the Northern Europe and the United States[26,27], and in Latin America and Southern Europe[28,29], respectively. Some predisposing factors including central venous catheters (CVC), total parenteral nutrition (TPN), and prior azole exposure are proposed to result in the emergence of non-albicans *Candida* species. Previous exposure to azole is particularly linked to isolation of *C. krusei* and *C. glabrata*[30].

Based on our practice, the incidence of *Candidemia*, and other fungal infections in Iran seem to be on a steep rise. A local epidemiological survey on IFIs in ICU and transplant wards in Iran suggested *C. albicans*, *Penicillium* spp., *Aspergillus niger*, and *Cladosporium spp.* as the most dominant isolates[31]. According to this report, environmental fungal contamination was found to be more prominent in ICU and the length of hospital stay in critical care setting was strongly associated with the colonization of fungi.

Another local epidemiology research on IFIs in pediatric patients with advanced kidney disease undergoing peritoneal dialysis and adults with kidney transplantation showed the significant impact of *Candidemia* on mortality and morbidity[32]. Furthermore, based on a

multi-center analysis on the prevalence of deep-seated mycosis in immunocompromised hosts in Tehran, Iran, *Candida* spp. were isolated in almost 70% of IFIs cases[33]. Of note, non-albicans spp. comprised almost one third of the *Candida* infections suggesting a possible clinical challenge with fluconazole-resistant *Candida* species[31-34]. The current state of our local epidemiologic insights on IFIs are in line with those of international reports[19,20,35-37]. Further research is needed to draw a clearer map about the incidence of IC and IA and the related subspecies in ICUs of different hospitals, cities and provinces all around Iran. There is an urgent need for institutions to set tight nosocomial IFIs surveillance and protective measures including hand hygiene and aseptic techniques especially upon bedside intensive care interventions.

DIAGNOSTIC CHALLENGES OF INVASIVE CANDIDIASIS IN THE INTENSIVE CARE UNIT

The diagnosis of IC can be either definitive or probable. The definitive diagnosis is based upon identification of *Candida* in the blood or its histological characterization in tissue[12]. However, in almost half of the instances, specimen may reveal false-negative results and the tissue may not be available in critical care setting. Moreover, awaiting culture results requires much time and defers the clinical decision making. Further to culture and tissue examination, some auxiliary testing methods and biomarkers such as 1-3 beta-D-Glucan (BDG) and pan-fungal polymerase chain reaction (PCR) may suggest probable IC when positive[38-40].

The BDG test detects beta-D-glucan which is an important constituent of the cell wall of pathogenic fungi. This test may however be a subject to a notable false-positive results in patients who receive albumin, immunoglobulins and beta lactams as well as those who are on hemodialysis with cellulose membrane[39]. Furthermore, the test is incapable to differentiate between *Candida* and *Aspergillus*, and remains inconclusive for *Zygomycetes* and *Cryptococcal* infection[39,41]. To indicate the probability of invasive candidiasis based on such a test, a single positive test lacks enough sensitivity thus serial measurements may be required. PCR which detects fungal nucleic acid is found to have a high sensitivity and specificity[42]. Although it is shown to be a highly promising tool in the diagnosis of IFIs, it is neither available nor validated in many settings and its exact use in clinic is questionable[38,43].

Given the time-consuming nature of all the aforementioned laboratory tests, and considering the critical time span for initialization of the therapy, the diagnosis of IC in ICU remains a challenge. Over the past decade some risk prediction models have put forward a pathway to identify patients at increased risk for IFIs. Evidence has suggested clinical benefits of empirical antifungal therapy in non-neutropenic critically-ill patients who remain febrile despite adequate antibiotic therapy and are characterized as high risk[7,8,11].

RISK STRATIFICATION TOOLS AND PREDICTIVE MODELS; PATH TO A TIMELY APPROACH

Prompt diagnosis and management of IC should be sought as it leads to a significant decline in human and cost burden in the ICU[26,27]. Potential risk factors for IC are compiled into risk prediction models. The proper use of these models in clinical practice would help clinicians identify the high-risk patients who significantly benefit from timely treatment against IC[10,11,44]. Meanwhile, the positive auxiliary tests such as BDG and/or PCR may further add to the accuracy of the risk prediction tools for IC[43,45,46]. Some of these validated tools include the Candida Score[9,47] and Ostrosky-Zeichner[23] model. Calculating the candida score assists a risk-factor-based prediction of IC depending on the presence or absence of four independent risk factors in febrile non-neutropenic critically-ill patients. These risk factors are severe sepsis (2 points), TPN (1 point), multifocal colonization (1 point), and surgery (1 point). The candida score of $\geqslant 3$ is shown to predict IC with a sensitivity and a specificity of 81% and 74%, respectively[9]. These "risk factors" which are proposed as Candida Prediction Rules have been reported in many other studies[47-53]. In addition to Leon's Candida Score[47] and the Ostrosky-Zeichner[23] model, other models such as Agvald-Ohman *et al*[48], Pittet *et al*[49], Hermsen *et al*[51], Paphitou *et al*[52], and Dupont *et al*[53] tried to establish similar frameworks putting together risk factors which contribute to IC while assigning separate relative risk scores for each variable. There is a visible overlap in considered risk factors among these models. Several differences in these studies make it difficult to draw a generally applicable conclusion. Figure 1 summarizes these risk prediction models with risk factors in common amongst them. According to these models, the most commonly considered risk factors such as TPN, use of wide-spectrum antibiotics, CVC, recent gastrointestinal (GI) surgery, use of steroids, dialysis and sepsis are regarded as the most significant contributors to IC in critical care units. Although fungal colonization is known to be linked with the development of *Candidemia*, based on more recent investigations, only a small proportion of colonized patients (3%-25%) are found to develop invasive candidiasis[48,54].

Some of the important differences in IC risk prediction models which are outlined in Figure 1 include the heterogeneity in the examined populations, non-similarity in the underlying disease severity, incidence of IC in centers where the investigations were carried out and the study end-points. It should be noted that most models were defined in surgical ICU populations[23,48,49,51-53].

Intra-abdominal infections secondary to intestinal perforations and anastomotic leakage are also among the risk factors in patients who tend to mostly benefit from

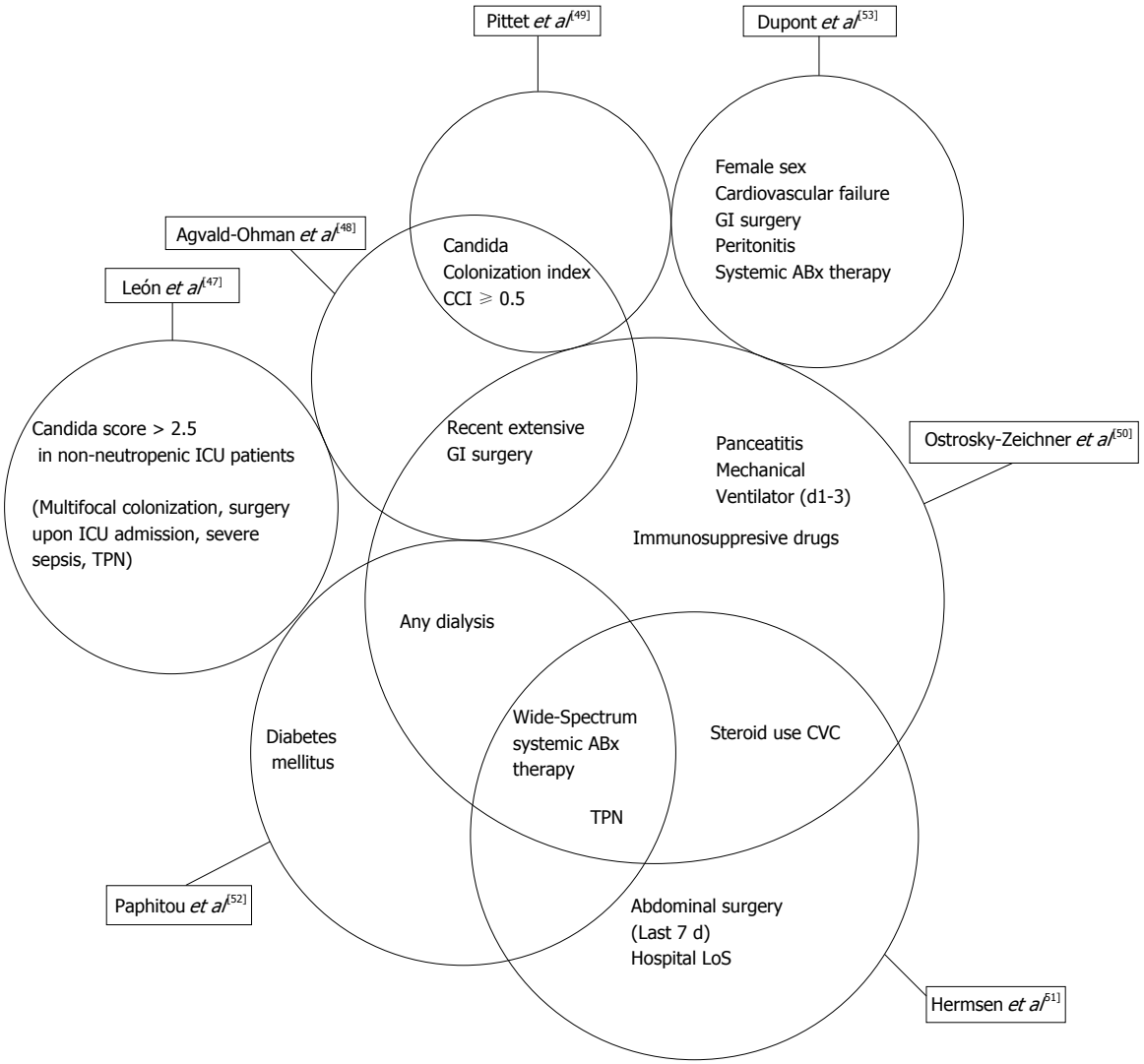


Figure 1 Risk prediction models for invasive candidiasis in critically ill patients with overlapping contributing factors. Factors which are common in several risk-prediction models appear to bear a higher relative risk for IC. Given the heterogeneity in study designs and populations, these models can hardly be merged to represent a single paradigm, however their common contributing factors appear to be of higher predictive value for IC prediction. So far, the most widely applied predictive tool for IC is the Leon's Candida Score followed by the Ostrosky-Zeichner's model. ABx: Antibiotic; CCI: Candida colonization index; CVC: Central venous catheter; GI: Gastrointestinal; ICU: Intensive care unit; TPN: Total parenteral nutrition; LoS: Length of stay.

timely antifungal therapy for IC[23]. Fluconazole (FCZ) has been the most abundant antifungal regimen used to treat IC. However the critical concern is the imprudent and wide usage of FCZ which has resulted in an increased resistance and the shift to non-albicans species[55]. Considering the emergence of different *Candida* species rather than *C. albicans*, a more justified approach should be sought to: 1-ensure the timely treatment of IC and 2-cover fluconazole-resistant *Candida* species.

APPROACH TO INVASIVE CANDIDIASIS IN INTENSIVE CARE UNIT

Treatment approaches towards IC in the ICU comprise prophylaxis, empirical-, preemptive- and targeted-therapy[56].

Prophylaxis, which is done to prevent IFIs development, is characterized as the use of antifungals in high-risk subjects in whom no sign or symptom of infection is so far documented. While FCZ is the main regimen used for this purpose, echinocandins (ECH) have recently been field tested with successful results[57].

On the other hand, initiation of antifungal agents in the presence of multiple risk factors and positive biomarkers such as BDG or PCR or other paraclinical findings is referred to as the pre-emptive treatment[56].

The time of treatment initiation is a key factor for the favorable outcome of IC[56,58]. According to several investigations[58-60], delayed antimicrobial therapy for more than 24 to 48 h negatively affects mortality. As such, in critically-ill or hemodynamically-unstable patients, late antifungal therapy may potentially predict death. Therefore, upon clinical suspicion for *Candidemia*, blood cultures need to be obtained and the treatment should to be administered without proof of IC based on the culture result[17]. This is generally referred to as the empirical approach. Prolonged length of stay in the ICU, surgery,

Table 1 Recommended treatment options for invasive candidiasis in adult non-neutropenic critically-ill patients based on the current international and local practice guidelines/consensus statements

Guideline	First choice	First alternative	Second alternative
ECCMID[15]	ECH	VCZ, L-AMB	FCZ
European experts opinion[16]	FCZ (stable patients and susceptible isolates) ECH (severe sepsis, micafungin last choice)	L-AmB	
IDSA[14]	FCZ (stable patients, azole naive) ECH (critically ill, Severe sepsis, recent azole exposure)	AmB or L-AmB	VCZ
Canadian practice guideline for invasive candidiasis in adults[17]	FCZ (stable patients, azole naïve) ECH (stable or unstable patients, recent azole exposure, avoid in *C. parapsilosis*)	AmB or L-AmB	
Consensus statement from the Iranian panel of experts[12]	FCZ (stable, No prior azole exposure, when hospital epidemiology indicates low incidence of NAC Spp.) ECH (hemodynamic instability, Fluconazole resistance)	VCZ, AmB or L-AmB (if available), considering the tolerability and cost *vs* utility	

ECCMID: European Congress of Clinical Microbiology and Infectious Diseases; ECH: Echinocandins; VCZ: Voriconazole; AmB: Amphotericin B; L-AmB: Liposomal Amphotericin B; FCZ: Fluconazole; IDSA: Infectious Disease Society of America; NAC: Non-albicans *Candida*.

multi-focal *Candida* colonization, sepsis, the use of TPN and/or wide-spectrum antibiotics are the key risk factors which warrant the empirical use of antifungals[14,56]. These are the risk factors considered in the "Candida Score"[47].

According to the latest international guidelines[14-17], the appropriate empirical antifungal choice greatly depends upon the local resistance patterns, likelihood of the presence of non-albicans species, hemodynamic status and criticality of the illness, prior exposure to azoles, pharmacodynamics and pharmacokinetics as well as the potential adverse effects of the selected antifungal, and last but not least, availability and cost of the treatment.

Based on the current guidelines, FCZ, ECH, amphotericin B (AmB) or its lipid formulations [Liposomal Amphotericin B (L-AmB)] and voriconazole (VCZ) are the recommended options while the first two are considered as the preferred choices in many instances. When the patient is hemodynamically unstable or has a prior exposure to FCZ with a high probability of non-albicans *candida* isolation (*i.e.,* or *C. glabrata* or *C. krusei*), echinochandins (*e.g.,* Caspofungin) are the preferred options[14,16]. AmB or L-AmB remain as alternative choices[14,17]. According to the Infectious Disease Society of America guideline, echinocandins should be taken as the first option in hemodynamically-unstable critically-ill patients[14]. Moreover, the most recent Canadian guideline contains similar recommendations about the critically-ill[17]. Caspofungin (CFG) is the only available echinocandin in our practice. De-escalation from CFG to FCZ is warranted in case of favorable clinical response and sterilization of blood cultures[12]. Based on the same guidelines, FCZ is suggested in hemodynamically stable cases without FCZ exposure over the last 30 d[14,15], meanwhile CFG is an equally suggested alternative[14,16,17]. Identification of local and general resistance patterns in our ICUs at different provinces would assist Iranian physicians to take more evidence-based decisions in their daily practice of IFIs management especially in the vulnerable critically-ill patients. In case of catheter-related BSI, an antifungal choice with activity against biofilm (*e.g.,* CFG or AmB) should be considered. CVCs should be removed at earliest. Generally, when the treatment is started, serial blood cultures should be taken to ensure blood sterilization. Treatment duration is 14 d after the negative blood culture[14,17].

Recommendations from the current international guidelines are summarized in Table 1. Table 2 demonstrates the dosing recommendations for the preferred options.

THE PANEL'S POSITION ON THE MANAGEMENT OF IC IN CRITICALLY-ILL PATIENTS

The current consensus roots in the earlier position statement from the Iranian experts in IFI-CF[12]. This report is considered as an updated recommendation for local practitioners who are involved in the management of IC critically-ill patients. Considering the limitations such as lack of availability or validity of fungal biomarker tests, narrow antifungal options and cost utility issue in our local practice, a customized format of international guidelines clinical pathway was drawn and agreed by the experts' panel. There is less focus on fungal biomarkers in this algorithm compared to the earlier consensus from the Iranian experts. Furthermore; prophylaxis, empirical, pre-emptive and targeted approaches are separately highlighted. The suggested clinical pathway is illustrated in Figure 2.

Some other issues including the importance of catheter removal, fundoscopic examination, frequency of blood cultures after the initiation of antifungal therapy, the possibility to draw a pathway for the patients without clinical response, and the subtype-specific antifungal therapy were also addressed by the panel. Below are some recommendations with regard to the above issues: (1) With respect to the clinical manifestations of suspected IFIs in the ICU and routine clinical evaluations, fundoscopic examination needs to be done by an intensivist. However, this examination has a low negative predictive value against IFIs and treatment should be based on a wider risk stratification and assessment; (2) In case of a documented IFI, catheter removal becomes mandatory

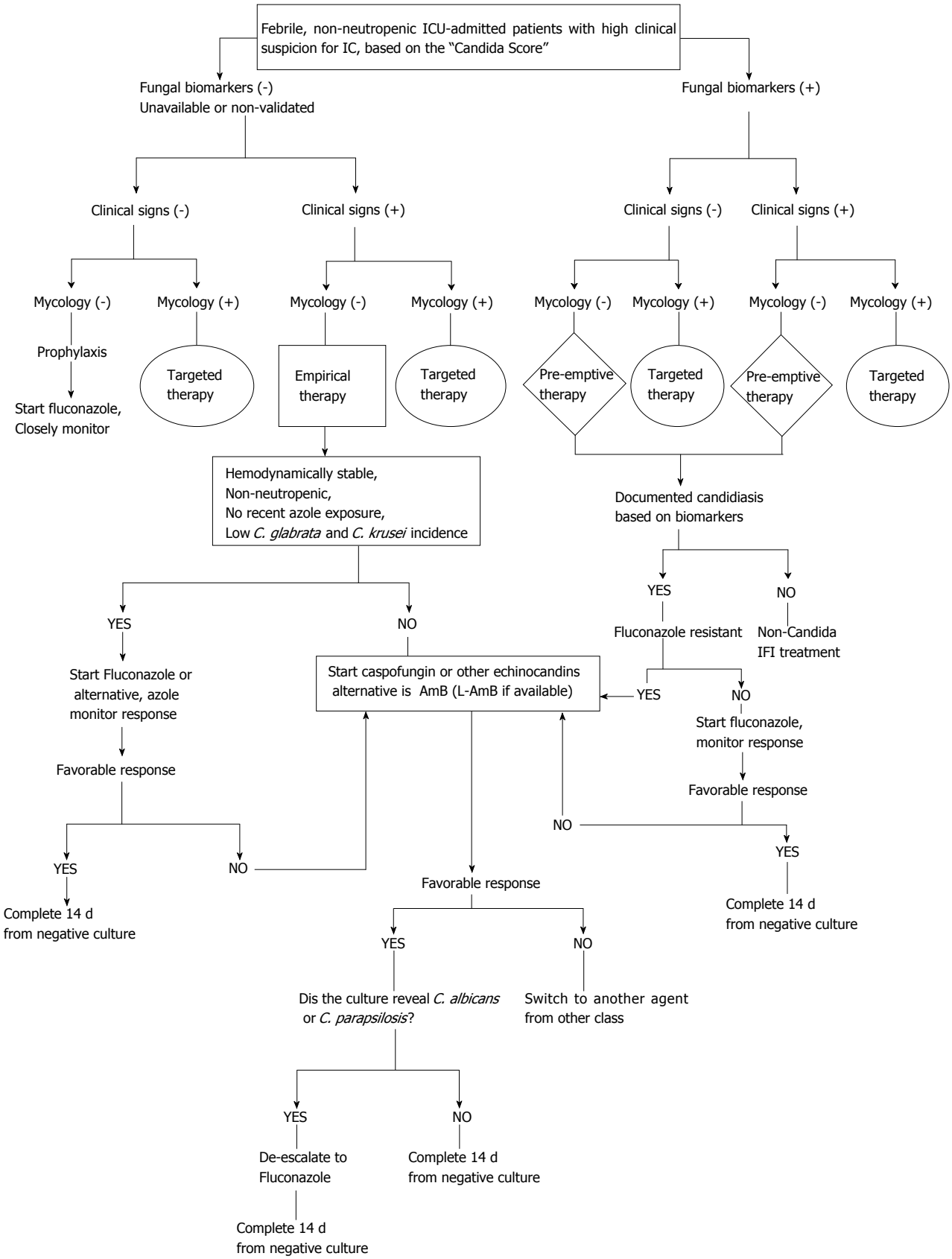


Figure 2 Management of invasive candidiasis in critical care setting. An updated consensus from the Iranian experts at invasive fungal infection-clinical forum. For justification and referencing see "diagnostic challenges of invasive candidiasis in the intensive care unit" and "approach to invasive candidiasis in intensive care unit" in the present report. IC: Invasive candidiasis; ICU: Invasive fungal infection; AmB: Amphotericin B; L-AmB: Liposomal Amphotericin B; IFIs: Invasive fungal infections.

Table 2 Recommended therapy with proper dosing in invasive candidiasis based on the current practice guidelines and consensus statements[12,14-16]

Recommended treatment	*Candidemia* (non-neutropenic patients, moderate to severe illness)	*Candidemia* (neutropenic patients)	Candida glabrata	Candida parapsilosis	Solid organ transplant recipients (prophylaxis)	ICU prophylaxis (high risk patients only)
Caspofungin	70 mg *iv* loading dose, then 50 mg/d per *iv*	70 mg *iv* loading dose, then 50 mg/d per *iv*	70 mg *iv* loading dose, then 50 mg/d per *iv*			
Micafungin	100 mg/d per *iv*	100 mg/d per *iv*	100 mg/d per *iv*			
Anidulafungin	200 mg/*iv* loading dose; then 100 mg/d per *iv*	200 mg/*iv* loading dose; then 100 mg/d per *iv*	200 mg/*iv* loading dose; then 100 mg/d per *iv*			
Fluconazole				800 mg *iv* loading, then 400 mg/d per *iv* or PO	200-400 mg/d *iv* or PO for 7-14 d	400 mg/d per *iv* or PO
(Alternative regimen) Fluconazole	800 mg *iv* loading, then 400 mg/d per *iv* or PO	800 mg *iv* loading, then 400 mg/d per *iv* or PO				
(Alternative regimen) Voriconazole if mold coverage is desired		6 mg/kg per *iv* q12h for 2 doses; then 4 mg/kg *iv* q12h or 200 mg PO q12h				
(Alternative regimen) Fluconazole or Voriconazole			With susceptibility testing			
(Alternative regimen) Echinocandins				If already responding to therapy		
(Alternative regimen) Liposomal Amphotericin B					1-2 mg/kg *iv*/d for 7-14 d	

ICU: Intensive care unit; PO: Per Os (Oral administration); *iv*: Intravenous.

since eradicating the infection without removing the device looks unlikely. The challenge will arise in the context of suspected IFIs in the presence of permanent catheters, pace makers, implantable cardioverter defibrillator or cardiac resynchronization therapy, *etc*. where some expert recommend a "device salvage trial" for successful outcome. Taken together, the general recommendation is to remove catheters the soonest possible; (3) The duration of antifungal therapy depends mainly on both response to treatment and status of blood culture at the beginning of IFI therapy. Normally, 72 to 96 h of treatment duration is adopted with a repeated blood culture after IFI therapy was started. The treatment will usually be stopped after 14 d since the first negative blood culture. If the therapy was started empirically (no positive blood culture), the duration of therapy is 14 d provided the patient's condition is improving on treatment. Repeated blood culture will prove whether the fungal infection is resolved; (4) Drawing a clinical pathway for non-responding patients may be difficult but still possible. Lack of response may be due to an alternative diagnosis, either non-fungal or additional microbial infections which have not been properly covered in the current therapy. Either way, a review has to be done to detect the possible source of infection and necessary investigations including standard blood cultures, non-culture based assessments, if available, and possible imaging studies such as high-resolution computed tomography and advanced ultrasound should be considered to diagnose a possibly-disseminated IFIs or resistant organisms not fully sensitive to the current therapy. In challenging, non-responding IFI cases, the treatment should be adjusted with the possibility of combination antifungal therapy. Finally, lack of response may be due to inappropriate source control including devices, foreign bodies, and surgically-accessible factors like collections which require appropriate interventions. One should always bear in mind that the lack of response may be due to non-infectious causes which also need to be well-explored; and (5) Based on the risk and severity assessment, empirical approach allows the timely management of IFIs. According to the evidence highlighted in this report, moderate- to high-risk patients for severe infections require echinocandins. Streamlining depends on response and the culture results. Meanwhile, mild infections in stable patients can still be treated with FCZ. Suspected *Aspergillus* requires VCZ, whereas the emerging and rare fungal infections would still require AmB. Furthermore, the possibility of combination antifungal therapy should be considered.

CONCLUSION

IC is a serious clinical condition with a notable risk of death in critically-ill patients when not treated properly. Increased awareness and practical insights through share of experience as well as adherence to international and local guidelines are key elements of success in the management of IC in the ICU.

According to the panel's opinion, LoS in the ICU and total days on mechanical ventilation, the presence of CVC/TPN, dialysis catheters, use of broad spectrum antibiotics, sepsis, presence of GI surgery, burn and high Acute Physiology and Chronic Health Evaluation II Score (> 16)[61] were considered as main risk factors justifying the empirical antifungal therapy against IC in febrile, non-neutropenic critically-ill patients admitted to the ICU.

The entire panel admitted that lack of experience and insufficient awareness is the main cause for delayed initiation of antifungal therapy in critically-ill patients. Meanwhile half of the participants believed that the paucity of diagnostic tools and inconsistent availability of the therapeutic options are crucial obstacles in parallel. All experts agreed that holding well-planned educational programs and fostering scientific activities within our IFI-CF will be a road to increase awareness and better practice with regard to the management of IFIs in critical care setting.

Upon conclusion, experts at the IFI-CF decided to continue holding regular meetings at institutional level in order to educate junior ICU staff and increase their awareness on the management of IC in the ICU.

The IFI-CF became determined to conduct biannual meetings to share experience and update local guidelines on IFIs management as required. In addition, utilizing the already established consensus, the experts agreed to pursue preparing printed protocols in each ICU in order to make it easier for the juniors to follow and implement.

ACKNOWLEDGMENTS

Authors would like to thank Dr. Dindoust P, Fahim R, Nabil Y, Nafarieh L and Salarian A for supporting this clinical forum. Appreciation is extended to Ms. Ranjbar E and Liaghi A for their invaluable assistance. This meeting received scientific and administrative support from Behestan Darou PJS and Behphar scientific Committee, Tehran, Iran.

REFERENCES

1 **Traynor K**. ICU infection-prevention efforts could be better, study finds. *Am J Health Syst Pharm* 2014; **71**: 444, 446 [PMID: 24589533 DOI: 10.2146/news140022]

2 **Hung CY**, Kao KC, Wang PN, Hu HC, Hsieh MJ, Fu JY, Chang CH, Li LF, Huang CC, Tsai YH, Yang CT. Invasive fungal infection among hematopoietic stem cell transplantation patients with mechanical ventilation in the intensive care unit. *BMC Infect Dis* 2012; **12**: 44 [PMID: 22339791 DOI: 10.1186/1471-2334-12-44]

3 **Martino R**, Lopez R, Sureda A, Brunet S, Domingo-Albós A. Risk of reactivation of a recent invasive fungal infection in patients with hematological malignancies undergoing further intensive chemo-radiotherapy. A single-center experience and review of the literature. *Haematologica* 1997; **82**: 297-304 [PMID: 9234575]

4 **Yu Y**, Du L, Yuan T, Zheng J, Chen A, Chen L, Shi L. Risk factors and clinical analysis for invasive fungal infection in neonatal intensive care unit patients. *Am J Perinatol* 2013; **30**: 589-594 [PMID: 23277386 DOI: 10.1055/s-0032-1329688]

5 **Ostrosky-Zeichner L**. Systemic antifungal therapy in patients without documented invasive fungal infection: a peek into the world of empirical antifungal therapy*. *Crit Care Med* 2012; **40**: 997-998 [PMID: 22343851 DOI: 10.1097/CCM.0b013e31823e9514]

6 **Zaragoza R**, Pemán J, Salavert M, Viudes A, Solé A, Jarque I, Monte E, Romá E, Cantón E. Multidisciplinary approach to the treatment of invasive fungal infections in adult patients. Prophylaxis, empirical, preemptive or targeted therapy, which is the best in the different hosts? *Ther Clin Risk Manag* 2008; **4**: 1261-1280 [PMID: 19337433 DOI: 10.2147/TCRM.S3994]

7 **Huibregtse JM**, Engelke DR, Thiele DJ. Copper-induced binding of cellular factors to yeast metallothionein upstream activation sequences. *Proc Natl Acad Sci USA* 1989; **86**: 65-69 [PMID: 2643107]

8 **Harrison D**, Muskett H, Harvey S, Grieve R, Shahin J, Patel K, Sadique Z, Allen E, Dybowski R, Jit M, Edgeworth J, Kibbler C, Barnes R, Soni N, Rowan K. Development and validation of a risk model for identification of non-neutropenic, critically ill adult patients at high risk of invasive Candida infection: the Fungal Infection Risk Evaluation (FIRE) Study. *Health Technol Assess* 2013; **17**: 1-156 [PMID: 23369845 DOI: 10.3310/hta17030]

9 **Paramythiotou E**, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: how to approach, how to treat. *Molecules* 2014; **19**: 1085-1119 [PMID: 24445340 DOI: 10.3390/molecules19011085]

10 **Leroy G**, Lambiotte F, Thévenin D, Lemaire C, Parmentier E, Devos P, Leroy O. Evaluation of "Candida score" in critically ill patients: a prospective, multicenter, observational, cohort study. *Ann Intensive Care* 2011; **1**: 50 [PMID: 22128895 DOI: 10.1186/2110-5820-1-50]

11 **Bruyère R**, Quenot JP, Prin S, Dalle F, Vigneron C, Aho S, Leon C, Charles PE. Empirical antifungal therapy with an echinocandin in critically-ill patients: prospective evaluation of a pragmatic Candida score-based strategy in one medical ICU. *BMC Infect Dis* 2014; **14**: 385 [PMID: 25015848 DOI: 10.1186/1471-2334-14-385]

12 **Ahmadi A**, Ardehali SH, Beigmohammadi MT, Hajiabdolbaghi M, Hashemian SM, Kouchek M, Majidpour A, Mokhtari M, Moghaddam OM, Najafi A, Nejat R, Niakan M, Lotfi AH, Amirsavadkouhi A, Shirazian F, Tabarsi P, Taher MT, Torabi-Nami M. Invasive candidiasis in intensive care unit; consensus statement from an Iranian panel of experts, July 2013. *JRSM Open* 2014; **5**: 2042533313517689 [PMID: 25057376 DOI: 10.1177/2042533313517689]

13 **Mardani M**, Tabarsi P, Yadegarinia D, Talebi Taher M, Najafi N, Hajabdolbaghi M, Rasoolinejad M, Badiei P, Janbakhsh A, Salehi H, Khorvash F, Aghazadeh K, Mansouri D, Namazi NMK. Treatment of invasive fungal infection: Recommendations from scientific leaders' meeting on November 3rd, 2011 tehran-iran. *Iran J Clin Infect Dis* 2011; **6**: 179-181

14 **Pappas PG**, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503-535 [PMID: 19191635 DOI: 10.1086/596757]

15 **Cornely OA**, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Flörl C, Petrikkos G, Richardson MD, Roilides E, Verweij PE, Viscoli C, Ullmann AJ. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012; **18** Suppl 7: 19-37 [PMID: 23137135 DOI: 10.1111/1469-0691.12039]

16 **Kullberg BJ**, Verweij PE, Akova M, Arendrup MC, Bille J, Calandra T, Cuenca-Estrella M, Herbrecht R, Jacobs F, Kalin M, Kibbler CC, Lortholary O, Martino P, Meis JF,

Muñoz P, Odds FC, De Pauw BE, Rex JH, Roilides E, Rogers TR, Ruhnke M, Ullmann AJ, Uzun Ö, Vandewoude K, Vincent JL, Donnelly JP. European expert opinion on the management of invasive candidiasis in adults. *Clin Microbiol Infect* 2011; **17** Suppl 5: 1-12 [PMID: 21884296 DOI: 10.1111/j.1469-0691.2011.03615.x]

17 **Bow EJ**, Evans G, Fuller J, Laverdière M, Rotstein C, Rennie R, Shafran SD, Sheppard D, Carle S, Phillips P, Vinh DC. Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis Med Microbiol* 2010; **21**: e122-e150 [PMID: 22132006]

18 **Gonçalves-Pereira J**, Pereira JM, Ribeiro O, Baptista JP, Froes F, Paiva JA. Impact of infection on admission and of the process of care on mortality of patients admitted to the Intensive Care Unit: the INFAUCI study. *Clin Microbiol Infect* 2014; Clin Microbiol Infect: [PMID: 24975209 DOI: 10.1111/1469-0691.12738]

19 **Castón-Osorio JJ**, Rivero A, Torre-Cisneros J. Epidemiology of invasive fungal infection. *Int J Antimicrob Agents* 2008; **32** Suppl 2: S103-S109 [PMID: 19013332 DOI: 10.1016/S0924-8579(08)70009-8]

20 **Cuenca-Estrella M**, Bernal-Martinez L, Buitrago MJ, Castelli MV, Gomez-Lopez A, Zaragoza O, Rodriguez-Tudela JL. Update on the epidemiology and diagnosis of invasive fungal infection. *Int J Antimicrob Agents* 2008; **32** Suppl 2: S143-S147 [PMID: 19013339 DOI: 10.1016/S0924-8579(08)70016-5]

21 **Hu R**, Jiang XY, Wu Y. Risk factors for invasive pulmonary fungal infection in patients with hematological malignancies not receiving hematopoietic stem cell transplant. *Neoplasma* 2012; **59**: 669-675 [PMID: 22862167 DOI: 10.4149/neo_2012_085]

22 **Sun YQ**, Xu LP, Liu DH, Zhang XH, Chen YH, Chen H, Ji Y, Wang Y, Han W, Wang JZ, Wang FR, Liu KY, Huang XJ. The incidence and risk factors of invasive fungal infection after haploidentical haematopoietic stem cell transplantation without in vitro T-cell depletion. *Clin Microbiol Infect* 2012; **18**: 997-1003 [PMID: 22085092 DOI: 10.1111/j.1469-0691.2011.03697.x]

23 **Ostrosky-Zeichner L**. Clinical prediction rules for invasive candidiasis in the ICU: ready for prime time? *Crit Care* 2011; **15**: 189 [PMID: 21943066 DOI: 10.1186/cc10422]

24 **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]

25 **Darouiche RO**. Candida in the ICU. *Clin Chest Med* 2009; **30**: 287-293, vi-vii [PMID: 19375635 DOI: 10.1016/j.ccm.2009.02.013]

26 **Gagne JJ**, Goldfarb NI. Candidemia in the in-patient setting: treatment options and economics. *Expert Opin Pharmacother* 2007; **8**: 1643-1650 [PMID: 17685882 DOI: 10.1517/14656566.8.11.1643]

27 **Falagas ME**, Apostolou KE, Pappas VD. Attributable mortality of candidemia: a systematic review of matched cohort and case-control studies. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 419-425 [PMID: 16773391 DOI: 10.1007/s10096-006-0159-2]

28 **Tragiannidis A**, Tsoulas C, Kerl K, Groll AH. Invasive candidiasis: update on current pharmacotherapy options and future perspectives. *Expert Opin Pharmacother* 2013; **14**: 1515-1528 [PMID: 23724798 DOI: 10.1517/14656566.2013.805204]

29 **Leroy O**, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, Carlet J, Reynes J, Rosenheim M, Regnier B, Lortholary O. Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). *Crit Care Med* 2009; **37**: 1612-1618 [PMID: 19325476 DOI: 10.1097/CCM.0b013e31819efac0]

30 **Playford EG**, Marriott D, Nguyen Q, Chen S, Ellis D, Slavin M, Sorrell TC. Candidemia in nonneutropenic critically ill patients: risk factors for non-albicans Candida spp. *Crit Care Med* 2008; **36**: 2034-2039 [PMID: 18552700 DOI: 10.1097/CCM.0b013e3181760f42]

31 **Kordbacheh P**, Zaini F, Kamali F, Ansari K, Safara M. Study on the sources of nosocomial fungal infections at intensive care unit and transplant wards at a teaching hospital in tehran. *Iranian J Publ Health* 2005; **34**: 1-8

32 **Hooman N**, Madani A, Sharifian Dorcheh M, Mahdavi A, Derakhshan A, Gheissari A, Esfahani ST, Otukesh H, Mohkam M, Falahzadeh MH, Hosseini Al Hashemi G, Azir A, Merikhi A, Golikhani F, Latif E, Karimi S, Zakavat T, Mohseni P, Ataei N, Nickavar A, Basiratnia M. Fungal peritonitis in Iranian children on continuous ambulatory peritoneal dialysis: a national experience. *Iran J Kidney Dis* 2007; **1**: 29-33 [PMID: 19357441]

33 **Bassiri Jahromi S**, Khaksar AA. Deep-seated fungal infections in immunocompromised patients in iran. *Iran J Allergy Asthma Immunol* 2005; **4**: 27-32 [PMID: 17301420]

34 **Naeini AE**, Sharifi M, Shahidi S, Taheri S, Seirafian S, Taheri D, Tazhibi M, Hejazi SH, Naini PE, Harandi AA. Intestinal fungal and parasitic infections in kidney transplant recipients: a multi-center study. *Saudi J Kidney Dis Transpl* 2012; **23**: 677-683 [PMID: 22805377 DOI: 10.4103/1319-2442.98110]

35 **Pfaller MA**, Andes DR, Diekema DJ, Horn DL, Reboli AC, Rotstein C, Franks B, Azie NE. Epidemiology and outcomes of invasive candidiasis due to non-albicans species of Candida in 2,496 patients: data from the Prospective Antifungal Therapy (PATH) registry 2004-2008. *PLoS One* 2014; **9**: e101510 [PMID: 24991967 DOI: 10.1371/journal.pone.0101510]

36 **Quindós G**. Epidemiology of candidaemia and invasive candidiasis. A changing face. *Rev Iberoam Micol* 2014; **31**: 42-48 [PMID: 24270071 DOI: 10.1016/j.riam.2013.10.001]

37 **Yapar N**. Epidemiology and risk factors for invasive candidiasis. *Ther Clin Risk Manag* 2014; **10**: 95-105 [PMID: 24611015 DOI: 10.2147/TCRM.S40160]

38 **Li Y**, Gao L, Ding Y, Xu Y, Zhou M, Huang W, Jing Y, Li H, Wang L, Yu L. Establishment and application of real-time quantitative PCR for diagnosing invasive aspergillosis via the blood in hematological patients: targeting a specific sequence of Aspergillus 28S-ITS2. *BMC Infect Dis* 2013; **13**: 255 [PMID: 23725402 DOI: 10.1186/1471-2334-13-255]

39 **Georgopapadakou NH**. Update on antifungals targeted to the cell wall: focus on beta-1,3-glucan synthase inhibitors. *Expert Opin Investig Drugs* 2001; **10**: 269-280 [PMID: 11178340 DOI: 10.1517/13543784.10.2.269]

40 **Jaijakul S**, Vazquez JA, Swanson RN, Ostrosky-Zeichner L. (1,3)-β-D-glucan as a prognostic marker of treatment response in invasive candidiasis. *Clin Infect Dis* 2012; **55**: 521-526 [PMID: 22573851 DOI: 10.1093/cid/cis456]

41 **Digby J**, Kalbfleisch J, Glenn A, Larsen A, Browder W, Williams D. Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. *Clin Diagn Lab Immunol* 2003; **10**: 882-885 [PMID: 12965921]

42 **Pfaller MA**, Diekema DJ, Rinaldi MG, Barnes R, Hu B, Veselov AV, Tiraboschi N, Nagy E, Gibbs DL. Results from the ARTEMIS DISK Global Antifungal Surveillance Study: a 6.5-year analysis of susceptibilities of Candida and other yeast species to fluconazole and voriconazole by standardized disk diffusion testing. *J Clin Microbiol* 2005; **43**: 5848-5859 [PMID: 16333066 DOI: 10.1128/JCM.43.12.5848-5859.2005]

43 **Ahmad S**, Khan Z, Mustafa AS, Khan ZU. Seminested PCR for diagnosis of candidemia: comparison with culture, antigen detection, and biochemical methods for species identification. *J Clin Microbiol* 2002; **40**: 2483-2489 [PMID: 12089267]

44 **Posteraro B**, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, Maviglia R, Fadda G, Sanguinetti M, Antonelli M. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index. *Crit Care* 2011; **15**: R249 [PMID: 22018278 DOI: 10.1186/cc10507]

45 **Goudjil S**, Kongolo G, Dusol L, Imestouren F, Cornu M,

Leke A, Chouaki T. (1-3)-β-D-glucan levels in candidiasis infections in the critically ill neonate. *J Matern Fetal Neonatal Med* 2013; **26**: 44-48 [PMID: 22913303 DOI: 10.3109/14767058.2012.722716]

46 **Tissot F**, Lamoth F, Hauser PM, Orasch C, Flückiger U, Siegemund M, Zimmerli S, Calandra T, Bille J, Eggimann P, Marchetti O. β-glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med* 2013; **188**: 1100-1109 [PMID: 23782027 DOI: 10.1164/rccm.201211-2069OC]

47 **León C**, Ruiz-Santana S, Saavedra P, Galván B, Blanco A, Castro C, Balasini C, Utande-Vázquez A, González de Molina FJ, Blasco-Navalproto MA, López MJ, Charles PE, Martín E, Hernández-Viera MA. Usefulness of the "Candida score" for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med* 2009; **37**: 1624-1633 [PMID: 19325481 DOI: 10.1097/CCM.0b013e31819daa14]

48 **Agvald-Ohman C**, Klingspor L, Hjelmqvist H, Edlund C. Invasive candidiasis in long-term patients at a multidisciplinary intensive care unit: Candida colonization index, risk factors, treatment and outcome. *Scand J Infect Dis* 2008; **40**: 145-153 [PMID: 17852926 DOI: 10.1080/00365540701534509]

49 **Pittet D**, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Ann Surg* 1994; **220**: 751-758 [PMID: 7986142]

50 **Ostrosky-Zeichner L**, Sable C, Sobel J, Alexander BD, Donowitz G, Kan V, Kauffman CA, Kett D, Larsen RA, Morrison V, Nucci M, Pappas PG, Bradley ME, Major S, Zimmer L, Wallace D, Dismukes WE, Rex JH. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis* 2007; **26**: 271-276 [PMID: 17333081 DOI: 10.1007/s10096-007-0270-z]

51 **Hermsen ED**, Zapapas MK, Maiefski M, Rupp ME, Freifeld AG, Kalil AC. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. *Crit Care* 2011; **15**: R198 [PMID: 21846332 DOI: 10.1186/cc10366]

52 **Paphitou NI**, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol* 2005; **43**: 235-243 [PMID: 16010850]

53 **Dupont H**, Bourichon A, Paugam-Burtz C, Mantz J, Desmonts JM. Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? *Crit Care Med* 2003; **31**: 752-757 [PMID: 12626979 DOI: 10.1097/01.CCM.0000053525.49267.77]

54 **Blumberg HM**, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT, Wenzel RP. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis* 2001; **33**: 177-186 [PMID: 11418877 DOI: 10.1086/321811]

55 **Vandijck DM**, Blot SI, Vandekerckhove L, Vogelaers DP. Fluconazole exposure and selection for Candida non-albicans. *Anesth Analg* 2008; **107**: 2091; author reply 2091-2092 [PMID: 19020168 DOI: 10.1213/ane.0b013e3181896c22]

56 **Mikolajewska A**, Schwartz S, Ruhnke M. Antifungal treatment strategies in patients with haematological diseases or cancer: from prophylaxis to empirical, pre-emptive and targeted therapy. *Mycoses* 2012; **55**: 2-16 [PMID: 21554421 DOI: 10.1111/j.1439-0507.2010.01961.x]

57 **Senn L**, Eggimann P, Ksontini R, Pascual A, Demartines N, Bille J, Calandra T, Marchetti O. Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients. *Intensive Care Med* 2009; **35**: 903-908 [PMID: 19172247 DOI: 10.1007/s00134-009-1405-8]

58 **Garey KW**, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, Bearden DT. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006; **43**: 25-31 [PMID: 16758414 DOI: 10.1086/504810]

59 **Morrell M**, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005; **49**: 3640-3645 [PMID: 16127033 DOI: 10.1128/AAC.49.9.3640-3645.2005]

60 **Garrouste-Orgeas M**, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, Lazard T, Jamali S, Mourvillier B, Cohen Y, De Lassence A, Azoulay E, Cheval C, Descorps-Declere A, Adrie C, Costa de Beauregard MA, Carlet J. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. *Clin Infect Dis* 2006; **42**: 1118-1126 [PMID: 16575729 DOI: 10.1086/500318]

61 **Muskett H**, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. *Crit Care* 2011; **15**: R287 [PMID: 22126425 DOI: 10.1186/cc10574]

P- Reviewer: Galgoczy L, Metan G, Mousavi SAA
S- Editor: Gong XM **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