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Peer Reviewer of *World Journal of Critical Care Medicine*, Rachid AIT ADDI, MD, PhD, Epidemiologist-Anthropobiologist, Research Scientist, Laboratory Associate member of Human Ecology, Department of Biology, University of Cadi Ayyad Marrakesh, Morocco. dr.rachid.aitaddi@gmail.com

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WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

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REVIEW

21st century critical care medicine: An overview

Smitesh Padte, Vikramaditya Samala Venkata, Priyal Mehta, Sawsan Tawfeeq, Rahul Kashyap, Salim Surani

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Smitesh Padte, Priyal Mehta, Sawsan Tawfeeq, Rahul Kashyap, Department of Research, Global Remote Research Scholars Program, St. Paul, MN 55104, United States

Vikramaditya Samala Venkata, Department of Hospital Medicine, Cheshire Medical Center/ Dartmouth Health, Keene, NH 03431, United States

Rahul Kashyap, Department of Research, WellSpan Health, York, PA 17403, United States

Rahul Kashyap, Salim Surani, Department of Pulmonary & Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Salim Surani, Department of Medicine & Pharmacology, Texas A&M University, College Station, TX 77843, United States

Corresponding author: Salim Surani, FCCP, MD, Professor, Department of Medicine & Pharmacology, Texas A&M University, 40 Bizzell Street, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

Critical care medicine in the 21st century has witnessed remarkable advancements that have significantly improved patient outcomes in intensive care units (ICUs). This abstract provides a concise summary of the latest developments in critical care, highlighting key areas of innovation. Recent advancements in critical care include Precision Medicine: Tailoring treatments based on individual patient characteristics, genomics, and biomarkers to enhance the effectiveness of therapies. The objective is to describe the recent advancements in Critical Care Medicine. Telemedicine: The integration of telehealth technologies for remote patient monitoring and consultation, facilitating timely interventions. Artificial intelligence (AI): AI-driven tools for early disease detection, predictive analytics, and treatment optimization, enhancing clinical decision-making. Organ Support: Advanced life support systems, such as Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy provide better organ support. Infection Control: Innovative infection control measures to combat emerging pathogens and reduce healthcare-associated infections. Ventilation Strategies: Precision ventilation modes and lung-protective strategies to minimize ventilator-induced lung injury. Sepsis Management: Early recognition and aggressive management of sepsis with tailored interventions. Patient-Centered Care: A shift towards patient-centered care focusing on psychological and emotional well-being in addition to medical needs. We conducted a thorough literature search on PubMed, EMBASE, and Scopus using our tailored strategy, incorporating keywords such as critical care, telemedicine, and sepsis management. A total of 125

articles meeting our criteria were included for qualitative synthesis. To ensure reliability, we focused only on articles published in the English language within the last two decades, excluding animal studies, *in vitro*/molecular studies, and non-original data like editorials, letters, protocols, and conference abstracts. These advancements reflect a dynamic landscape in critical care medicine, where technology, research, and patient-centered approaches converge to improve the quality of care and save lives in ICUs. The future of critical care promises even more innovative solutions to meet the evolving challenges of modern medicine.

Key Words: Critical care medicine; Intensive care unit; Precision medicine; Telemedicine; Artificial intelligence; Organ support; Sepsis; Infection control; Patient-centered care

Core Tip: In 1959, the first modern critical care unit, led by Dr. Peter Safar, emerged at the University of Pittsburgh, as detailed in the American Thoracic Society Journal. Critical care medicine has since expanded from traditional hospital settings to include emergency departments, ambulances, and even aircraft. The advent of the 21st century has ushered in notable advancements, including enhanced ventilation and organ support systems such as extra-corporeal membrane oxygenations, or even integrating telemedicine to extend critical care expertise to remote regions. In this dynamic environment, staying abreast of innovations such as artificial intelligence, precision medicine, nanotechnology in sepsis management, and inventive infection control strategies is crucial for reshaping our intensive care units. Our goal, amid these advances, is to provide a comprehensive overview of 21st-century progress in critical care, offering succinct insights on various specific topics in critical care medicine.

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INTRODUCTION

Critical care medicine has been defined by multiple entities. According to the American College of Physicians, it is defined as clinical care consisting of the diagnosis and treatment of a wide variety of clinical problems representing the extremes of human disease[1]. Villar *et al*[2] defined it as medicine that has the capacity to reverse near-fatal disease states, providing temporary support to the vital organ system while the patient recovers from the underlying disease processes.

Foundations of critical care medicine were laid in the mid-20th century with the initiation of mechanical ventilation, and continuous monitoring of physiological parameters while providing care to the critically ill[3]. Since the advent of the 21st century, there have been significant advances in this field leading to better outcomes for critically ill patients[4-6]. These advances include better ventilation strategies to prevent lung injury, the initiation of advanced life support systems such as Extra Corporeal Membrane Oxygenation (ECMO), and better management of sepsis syndromes with earlier interventions among others. With the incorporation of technology such as telemedicine into critical care, it has been made possible to provide necessary critical care expertise in rural areas who otherwise would not have access to it. In this ever-evolving landscape, contemporary critical care practitioners are confronted with the formidable task of keeping abreast of the latest advancements and innovations in their field, amidst the vast array of research articles and educational initiatives available. In addition to these challenges and advancements, the integration of artificial intelligence (AI) and the emergence of precision medicine has begun to reshape the intensive care unit (ICU) landscape[7].

Our aim, considering these developments, is to provide a comprehensive overview of progress made in the 21st century in the multidisciplinary field of critical care. By offering concise descriptions of select articles categorized by specific advances, our goal is to provide fundamental insights into the cutting-edge strides made within this domain. Ultimately, we hope to inspire our readers to delve into the original articles for a deeper understanding of the evolving landscape of critical care. The flow diagram of included studies is listed in Figure 1.

DISCUSSION

Precision medicine

The beginning of the 21st century marked the completion of the Human Genome Project in 2003 and ushered in the hope that medical care could be tailored to an individual using their DNA[8]. However, it wasn't until 2009 that the term "precision medicine" was first coined[9]. This was closely followed by the emergent growth of P medicine – Personalized, Precision, Preventive, Predictive, Pharmacotherapeutic, and Patient Participatory Medicine[10]. The term, broadly

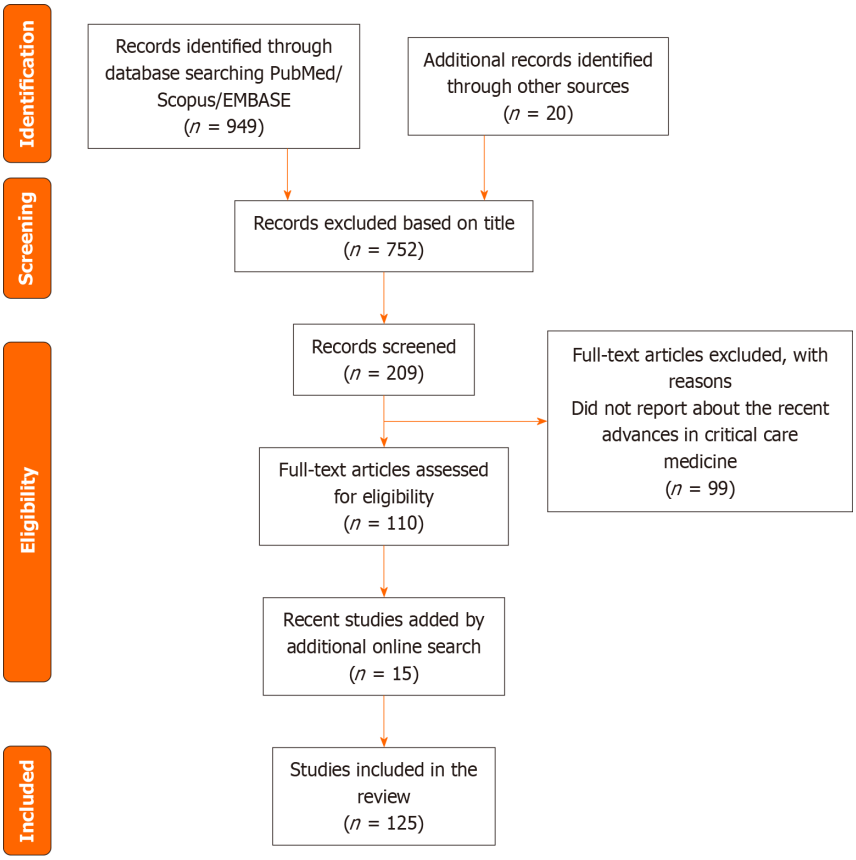

Figure 1 Flow diagram of included studies.

constructed, describes an approach to disease prevention and treatment that exploits the multiple distinct characteristics of individuals[11]. Despite multiple definitions existing, the Institute of Precision Medicine defined it succinctly "Precision medicine is targeted, individualized care that is tailored to each patient based on his or her specific genetic profile and medical history." The advances in precision medicine have their roots in oncology but recent developments have seen them make their way into critical care medicine[12].

Genomics and precision medicine go hand in hand as they focus on the individual's unique heritable characteristics. Recent interest in genomics has gradually increased, with multiple genome-wide association studies and large-scale projects gaining relevance. The International Hap-Map Project, the Precision Medicine Initiative (PMI) in the United States, and the 10000 Genome Project in Great Britain reflect that perhaps the key to precision medicine lies in our genes [11,13].

Recent advances have been hopeful. A retrospective study on 167 trauma patients showed that when a set of 63 genes were incorporated into the genomic score, they appeared to perform better in predicting outcomes than the Injury Severity Score and the Acute Physiology and Chronic Health Evaluation II (APACHE-II) (VSV1) metric[14-16]. Gene expression analyses have also been successful in distinguishing the molecularly defined subtypes of sepsis and even estimating their responses to various treatment modalities, such as corticosteroid therapy[11]. Efforts to simplify genetic signatures have led to the identification of an 11-gene signature that can be used to distinguish sepsis from other non-infectious states. Similarly, a two-gene signature was used to classify pediatric infections as either viral or bacterial in origin[11]. A multi-pronged approach to identifying the Single Nucleotide Polymorphisms responsible for the development of acute respiratory distress syndrome (ARDS) from pulmonary or extra-pulmonary causes directed us toward the role of FAAH and the POPDC3 gene[8]. Despite the ever-advancing research, the clinical application of these studies remains uncertain.

Biomarkers in critical care play the all-important role of bringing precision medicine from research papers to the intensive care unit[17]. The value of biomarkers in the ICU lies in their ability to predict the prognosis or even assess the efficacy of a treatment line. There has been much excitement surrounding them, with multiple new biomarkers being studied for the two prototypical ICU Illnesses - ARDS and Sepsis[11].

Acute respiratory distress syndrome

Serum markers have shown reasonable success in classifying ARDS based on the etiology (direct vs. indirect lung injury) [11,18]. The ARMA Trial showed that elevated levels of Von Willebrand (VWf) protein, soluble tumor necrosis factor receptors 1 and 2 (sTNFr), plasminogen activator inhibitor-1 (PAI-1) and plasma surfactant protein-D (SP-D) have all been independently associated with worse outcomes in ARDS[19]. A higher baseline plasma soluble receptor for advanced glycation end products was linked to an increased risk of 90-d mortality, according to a meta-analysis of eight studies [19]. Similarly, higher tumor necrosis factor-α and Interleukin 1-β levels in Broncho-Alveolar Lavage Fluid have been

associated with the development of ARDS in at-risk patients[8].

Sepsis

Around 180 biomarkers have been studied in sepsis and septic shock[8]. For the early detection of sepsis, the following five biomarkers were shown to have a sensitivity and specificity of over 90%: Interferon-induced protein (IP)-10, Group II phospholipase (PLA2-II), CD64, and CD11b. PLA2 and CD64 are the only ones that have demonstrated encouraging outcomes in adult patients[8]. In recent years, procalcitonin has also become a biomarker that is increasingly popular in differentiating between bacterial infection and sepsis for better diagnostic accuracy[17]. Additional predictive biomarkers for higher mortality in sepsis include angiopoietin-1 and angiopoietin-2, plasma cell-free host DNA, and IL-6 and IL-8 [19]. Multi-marker panels are also under investigation, aiming to provide a more comprehensive understanding of complex conditions like sepsis[20-22]. While biomarkers hold great potential, their widespread clinical use still faces challenges and requires further research to fully harness their diagnostic and prognostic capabilities.

Tele-ICU

As per the Centers for Medicare and Medicaid Services, telemedicine is defined as two-way real-time interactive communication between a patient and a physician or practitioner at a distant site through telecommunications equipment that includes audio and visual equipment[23]. Telemedicine is the diagnosis and treatment of patients over long distances using communication technologies[24]. In the critical care setting/Intensive care unit, critical care services offered *via* telemedicine are known as Tele-ICU or Tele-Critical Care[17]. Even though evidence regarding mortality benefits of 24 × 7 intensivist coverage (both day and nighttime) in the ICU reports mixed results, studies indicate improved mortality rates with high-intensity ICU coverage (mandatory consultation with an intensivist or transfer of care to an intensivist-led team) when compared to low-intensity coverage (optional consultation with the intensivist)[25-27].

Unfortunately, the worsening shortage of intensivists in the United States prevents hospitals nationwide from providing full-time intensivist coverage in the ICU. Tele-ICU has emerged as an alternative model to provide critical intensivist services to hospitals[28-30]. Patients on continuous monitors can be reviewed by remote critical care clinicians, enabling the early identification of emerging health issues[30]. Clinicians can then communicate with on-site care teams to initiate necessary interventions promptly. In addition, the application of tele-critical care has been shown to reduce hospital transfers and improve patient outcomes in sepsis[31].

With the advancement of communicative technologies in the 1970s, early consultative telemedicine critical care services were used unsuccessfully in 1982 by Grundy *et al*[32]. As technology continued to improve, in 2000 Rosenfeld *et al*[29] at Johns Hopkins conducted a 16-wk trial of telemedicine on ICU patients and reported improved patient mortality rates. They concluded that telemedicine critical care services can be offered with improved patient outcomes.

Since these studies were done and with the advancement of technological services, Tele-ICU use has grown across the United States. Kahn *et al*[33] looked at data from the Centers for Medicare and Medicaid Services between 2003-2010, they reported that the number of hospitals using Tele-ICU increased from 16 (0.4% of the total) to 213 (4.6% of the total) and the number of beds covered by telemedicine increased from 598 (0.9%) to 5799 (7.9%).

Over the past two decades, multiple studies have been done looking at outcomes with Tele-ICU. Even though initial studies looking at a few hundred patients show mixed results in terms of mortality, recent multiple larger studies indicate improved outcomes including ICU mortality and length of stay. A meta-analysis done by Young *et al*[34] in 2011 and Chen *et al*[35] in 2017 that looked at 41374 and 192265 patients respectively showed improved ICU mortality and length of stay with Tele-ICU. Similarly, a review done by Mackintosh showed improved patient mortality with Tele-ICU[36].

The major barrier with Tele-ICU is the costs ($50000-$100000 per bed)[37]. Despite this, as the physician shortage is expected to worsen, Tele-ICU shows promising results as a potential alternative to provide much-needed critical care services in hospitals around the country.

AI

AI constitutes the set of algorithms that enable machines to reason and execute tasks that include problem-solving, object and word recognition, state inference, and decision-making[38]. It expands upon Machine Learning *via* Artificial Neural Networks by utilizing tensors for "Deep Learning" (DL). As opposed to a sole clinician, DL can efficiently process multiple inputs, programming complex non-linear relationships to generate individualized prediction models[39]. In 1981, logistic regression was applied to validate the APACHE score, signifying the first use of AI in critical care medicine to support clinical decisions[40].

Featuring two super learner prediction models, SL1 and SL2, Pirracchio *et al*[41] introduced a novel mortality prediction algorithm for ICU patients in 2015. Compared to the Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II) scores, it displayed greater efficacy in predicting early mortality[42]. In addition, the United States Food and Drug Administration has authorized the clinical application of certain healthcare products, such as image analysis software (*e.g.*, DeepRhythmAI[43] by Medicalgorithmics SA) and basic cardiopulmonary function monitoring software (*e.g.*, IRNF App by Apple Inc. and Air Next by NuvoAir AB)[40]. Jiao *et al*[44] developed an AI system for predicting the prognosis of coronavirus disease 2019 (COVID-19) patients based on chest X-rays. The model exhibited significantly better prognostic performance compared to conventional severity scores in both internal and external testing. AI-based tools for rapid COVID-19 diagnostics have been developed, including those by Mount Sinai Health System and the University of Minnesota, in collaboration with Epic Systems and M Health Fairview[45]. Software predictors, like COViage[46] and the CLEWICU System[47], identify high-risk patients for clinical events such as intubation, respiratory failure, and low blood pressure. Additionally, adherence to AI-specific reporting guidelines like SPIRIT-AI[48], CONSORT-AI, and HUMANE can enhance AI application development and quality[49].

AI-guided tools for sepsis have shown promise as well. Earlier detection *via* sepsis surveillance algorithm has been a pioneering advancement in the 21st century[50]. Automation of sepsis clinical data abstraction *via* computable phenotype is crucial in sepsis care and research[51]. A reinforcement learning model improved mortality when clinical decisions aligned with the model's suggestions[52]. Predicting changes in urine output after fluid administration, an essential end-organ perfusion indicator, achieved an area under the curve of 0.86 using a gradient-boosting algorithm[52,53]. AI-guided POCUS can even enhance inter-operator reliability[54]. Machine learning holds the potential for enhancing sepsis management and volume responsiveness prediction in the ICU in this new century.

In a complex ICU setting with challenging staff and resource management, AI can enhance disease prognostication for informed decision-making[45]. Elhazmi *et al*[55] utilized a decision tree to predict COVID-19 patients' 28-d ICU mortality. It proved useful for identifying individuals at high risk. Leveraging a cohort of 289351 COVID-19 patients, Lazzarini *et al*[56] introduced the "Gradient Boosting Decision Tree" machine learning model that predicts severe COVID-19 cases, demonstrating its superior performance compared to older models and even human experts in terms of precision and recall.

Language learning models like Chat-GPT/GPT-4 have the potential to assist clinical judgment under intensivist supervision, improving clinical decision support optimization, as well as in clinical research in critical care[57]. Its applications extend to ECMO management, education, weaning, and decision-making[57]. Furthermore, it could be applied to other commonly used ICU medical equipment such as ventilators, defibrillators, electrocardiograms, or critical care radiology workflow[58]. While the model displays a capacity to learn and adapt, it has certain limitations in terms of medical expertise[45].

Challenges in applying machine learning (ML) in intensive care include poor data quality, ethical and legal concerns, and the absence of specific educational programs[59]. Most ML algorithms lack external validation, and real-world performance issues, like the EPIC sepsis-alleviation system, highlight practical hurdles. A vast majority of ML studies in intensive care are retrospective, with limited evaluation in clinical practice[45]. Inclusive datasets are crucial for AI model applicability, but transparency and legal guidelines are vital for trust and accountability[52]. Despite challenges, AI is poised to grow in its role in critical care in the future.

Organ support

Extra corporal membrane oxygenation: The ECMO is a device that temporarily replaces the heart and lung function *via* gas exchange through an extracorporeal circuit, while the patient is being resuscitated from underlying cardiopulmonary pathology[60]. In addition to providing respiratory and circulatory support, one of the main goals of ECMO is to prevent ventilator-induced lung injury which is a major cause of mortality in this population[61]. This feature of ECMO is thought to be more important in improving outcomes than providing oxygenation support[60,61].

ECMO technology was developed in the 1960s and used on humans for the first time in the 1970s[62,63]. Due to the advancement of technology, new extracorporeal circuit design, and better ventilation strategies, observational studies started reporting promising results in terms of survival outcomes[64,65]. In 2009 multicenter randomized controlled trial (RCT) done by Peek *et al*[66] reported improved outcomes with ECMO compared to conventional management. Even though the results of the Conventional ventilatory support *vs* extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial[66] were controversial, these studies led to renowned interest in ECMO. This along with continuing development in technology led to an increase in the use of ECMO worldwide[67,68]. As of 2015, more than 78000 cases have been reported to the Extracorporeal Life Support Organization (ELSO) and the number of hospitals reporting to ELSO has been steadily rising[68]. Meta-analysis of RCT done by Munshi *et al*[69] in 2019 published in the Lancet showed reduced 60-d mortality when compared to mechanical ventilation. With recent studies showing strong evidence in favor of ECMO, even after cardiopulmonary resuscitation and with ongoing advances in technology ECMO will likely be the standard of care in the future, if not already for ICU patients who meet the ECMO support initiation criteria[70].

Continuous renal replacement therapy

Dialysis, an external machine that can serve as renal replacement therapy, was initially conceptualized in 1854 by Thomas Graham and was first used in patients in 1945 by Dr. William Koff. Since then with advances in technology and techniques, dialysis has become the standard of care for renal replacement in patients with renal failure[71]. Traditional dialysis is performed intermittently, typically a few days a week. In 1977 Peter Kramer performed the first continuous arteriovenous hemofiltration (CAVH), with the main advantage being hemodynamic stability even in critically ill patients (VSV3)[72,73]. With technological advancements, CAVH has paved the way for development of present-day continuous veno-venous hemofiltration (CVVH).

In addition, over a 48-h period CVVH leads to a higher net fluid removal compared to regular dialysis, so it has shown to be beneficial in critically ill patients requiring large-volume fluid resuscitation[74]. Another advantage of CVVH would be in patients with cerebral edema, ischemic heart disease (IHD) may lead to hypotension and consequent compensatory cerebral vasodilation. Also, the rapid removal of urea with IHD can lead to water shifting into the cellular space[74,75]. Despite the ambiguity of survival benefit with CVVH compared to IHD. There are clear advantages with CVVH compared to IHD in specific critically ill patients and it's been used widely in intensive care units since the beginning of the 21st century.

Infection control

In the ICU, 19.2% of patients develop infections, compared to 5.2% in other hospital wards[76]. On any given day, about one in 31 hospital patients has at least one healthcare-associated infection[77]. Mucosal disruption, immune suppression,

invasive devices, surgery, antibiotic use, and encounters with multidrug-resistant pathogens are all contributing factors.

Effective prevention measures including universal gloving, gowns, masks, and hand hygiene have been used since the inception of critical care, but they can be time-consuming[78]. Electronic monitoring tools for hand hygiene, like Electronic Hand Hygiene Monitoring Systems (EHHMS), are increasingly used to capture and promote compliance in the 21st century[79]. While direct observation is the gold standard, EHHMS offers larger and less biased data sets, reducing the Hawthorne effect and providing a more comprehensive view of compliance[80].

In the past two decades, healthcare worker (HCW) vaccination against nosocomial infections has gained prominence [79]. Since July 2007, the Joint Commission has mandated annual influenza vaccination programs in healthcare facilities. Pertussis vaccination for HCWs was recommended due to the rising incidence. Similarly, COVID-19 vaccines became mandatory to curb the pandemic since the year 2020[81]. Biocontainment facilities have become essential for managing infectious diseases like the Ebola virus while minimizing transmission risks in the 21st century[82].

Viana Martins *et al*[83] made a crucial development in the COVID-19 fight by highlighting the efficacy of UV-C devices in inactivating the airborne severe acute respiratory syndrome coronavirus. The BETR Disinfection Study[84] from 2016 influenced healthcare facilities to adopt UV-C as a standard method for multidrug-resistant infections. However, Rock *et al*[85] found UV-C disinfection did not reduce certain infections in immunocompromised patients. Nonetheless, UV-C disinfection remains crucial in preventing other healthcare-associated infections. Novel technologies that enhance environmental decontamination, like hydrogen peroxide vapor, ultraviolet light, self-disinfecting surfaces, antimicrobial textiles, and sporicidal disinfectants, effectively combat contamination and minimize infection risks in the 21st century and are expected to advance further[79].

With the increasing use of electronic health record systems in the past two decades, electronic orders and reminders have become essential tools for curbing Catheter-Associated Urinary Tract Infections[80]. They prompt appropriate urinary catheter use and prompt removal, significantly reducing infection rates. Decision-support tools, such as electronic nudges and hard stops, steer clinicians away from choices that may heighten HAI risk. These tools are invaluable in the era of rapid infectious disease spread.

Digital polymerase chain reaction has emerged as a promising diagnostic technology in the past 20 years. It aids in the early identification of microbial genes, quantifies microbial burden, and explores host responses, making it a valuable tool in diagnosing and differentiating conditions like sepsis from systemic inflammatory response syndrome (SIRS)[86]. Moreover, predictive modeling using machine learning is revolutionizing infection prevention. Recent studies demonstrate its potential in assessing patients' risk of central line-associated bloodstream infections, ventilator-associated pneumonia, C. difficile infections, and catheter-associated urinary tract infections. Some models outperform traditional regression methods[79]. More testing and validation are underway to incorporate these new advances into practice.

Ventilation strategies

Mechanical ventilation (MV) is a lifesaving intervention that provides temporary oxygenation and ventilation for patients with respiratory failure until the underlying pathology is treated. It consists of invasive and non-invasive MV. Invasive MV consists of an endotracheal tube placed in the patient's trachea through the mouth or nose. This tube is connected to a ventilator which delivers a set amount of oxygen and a number of breaths per minute[87]. Non-invasive ventilation (NIV) consists of a machine that delivers a set amount of oxygen and ventilatory breaths *via* an external mask[87].

Invasive mechanical ventilation

The 21st-century ventilators have the option of various ventilation modes[88]. Volume limited, Pressure Limited, and Pressure Support (PSV) are the three main modes of ventilation. In volume limited, inspiration ends after a set inspiratory volume, in pressure limited inspiration ends after a set inspiratory pressure. Each mode has its advantages and can be used in specific patient situations. With PSV ventilation mode, once a breath is triggered by the patient, inspiratory pressure is delivered until the inspiratory flow decreases to a predetermined percentage of its peak value.

Ventilation in ARDS

Enhancing ventilation strategies for ARDS patients is one of the more significant advances in the field of critical care over the past two decades and it has led to improved patient outcomes. The landmark ARDSnet trial in 2000 demonstrated that lower tidal volume ventilation (6 mL/kg) in ARDS patients leads to lower mortality and an increased number of days without ventilator use[89]. This was subsequently supported by multiple studies which reported similar results[90-92].

As of the year 2023, low tidal volume ventilation (LTV) should be the standard of care for ARDS patients around the world. Despite the existing evidence, studies suggest that low tidal volume ventilation in ARDS patients is underutilized. In a multicenter observational study of ARDS patients around the United States showed that LTV was utilized in only 30% of the cases. Awareness needs to be raised and there needs to be a standardized institutional protocol to improve compliance with LTV[92].

Non-invasive ventilation

Numerous studies conducted at the onset of the 21st century have confirmed the efficacy of NIV in COPD exacerbation[93, 94]. As per the latest American Thoracic Society/European Respiratory Journal guidelines in the year 2017, NIV is indicated in specific patients with acute respiratory failure secondary to COPD exacerbation and cardiogenic pulmonary edema[95].

Sepsis management

Sepsis, a life-threatening organ dysfunction from an infection-triggered host response, presents a rising global challenge. Incidence has steadily increased since 1991, causing about 49 million sepsis cases and 11 million deaths in 2017[96]. Despite therapeutic progress, septic patients face high in-hospital mortality, comprising 20% of all global deaths. The Surviving Sepsis Campaign (SSC) started at the dawn of 21st century in the year 2003, uniting medical societies across the globe to create guidelines for reducing sepsis mortality[97]. Conventional therapies center on fluids, source control, and antimicrobials. With the initiation of Surviving Sepsis Campaign, indicators like central venous pressure and central venous oxygen saturation were added to the definition to help with the diagnosis[97,98]. These guidelines have been continuously updated, with the latest in 2021[99]. The evolving care bundles with shorter time frames (from 3-6-h bundles to 1-h bundles) for sepsis, emphasizing rapid recognition and resuscitation, place emergency physicians in a critical role[98,100]. The third re-definition in 2016 was done to improve the specificity of the old definition of Sepsis [101]. In this latest definition terms like SIRS, Severe Sepsis were removed. Sepsis-related quick SOFA (qSOFA) was introduced[102] as per the latest update. Screening tools like SIRS, MEWS, NEWS, and qSOFA help identify septic patients[103]. Below are the main advances in various aspects of sepsis management over the past two decades.

Antimicrobials

Since 2004, sepsis management guidelines recommended the initiation of antibiotic therapy within one hour of the presentation of patients with severe sepsis and septic shock in the ICU[104]. Multiple large studies have demonstrated increased mortality with each hour of delay in antibiotic administration in this population[105,106].

As per the latest SSC guidelines, in patients with sepsis or septic shock therapy initiation covering all likely pathogens and antibiotic coverage, once the pathogen is identified has been a cornerstone management in this century[102]. In the current standard of care, most patients with sepsis shock receive anti-pseudomonal antibiotic coverage[107] as part of empiric antibiotic therapy[100].

Intravenous fluid

Based on Rivers *et al*[108], SSC had initially recommended fluid bolus administration as an integral component of sepsis management[104,108]. After this over the past two decades, multiple large trials[109-112] and studies have shown variable results in outcomes between EGDT and usual therapy. Taking all the existing evidence into consideration, SSC guidelines currently recommend 30 mL/kg bolus as part of resuscitation from sepsis-induced hypoperfusion.

Even though guidelines do not recommend a specific type of intravenous fluid in sepsis, evidence indicates improved mortality with the use of balanced crystalloids such as lactated ringer, and plasmalyte compared to normal saline[113]. Additionally, albumin inclusion during resuscitation has no impact on sepsis or septic shock mortality[114].

Experimental therapies

Innovative approaches in the 21st century target immune balance through extracorporeal therapies (ECT) or blood purification for sepsis care[115]. ECT aims to reduce inflammatory mediators and toxins, achieving immune balance and homeostasis. Removing peak cytokine levels in early sepsis, per the 'cytokine peak concentration' hypothesis, can limit organ damage and multi-organ dysfunction syndrome. ECT methods include convection therapies (CRRT, HVHF, HCO), adsorption therapies (*e.g.*, Polymixin B, CytoSorb®), and combination therapies[115]. The Molecular Adsorbent Recirculating System (MARS™) supports the liver by removing albumin-bound toxins, showing short-term benefits in hepatorenal syndrome and hepatic encephalopathy[116]. "Externally modulated electric-based devices" sense and target endotoxins with antibiotics to curb inflammation[117]. A lipopolysaccharide (LPS) neutralizing cartridge detects and neutralizes LPS, combining antibiotic and anti-inflammatory effects.

Recent advances in critical care technology have introduced hemodynamic monitoring tools like pulse contour analysis, which calculates cardiac output from arterial line data. Various invasive and noninvasive markers, including end-tidal CO2, inferior vena cava collapsibility index, and point-of-care ultrasound (POCUS), are evaluated for sepsis [118]. POCUS offers rapid LV and RV function assessments, even remotely. Venous Doppler waveform analysis and the venous excess ultrasound score help predict venous congestion severity. However, POCUS alone can't replace a comprehensive cardiovascular assessment. It is being considered alongside clinical parameters.

Recently, nanomaterial strategies have offered a more versatile tool for sepsis management. They serve as inherent therapeutics or nanocarriers for precise agent delivery. These formulations possess antibacterial, anti-inflammatory, immunomodulatory, and anti-oxidative effects, providing a multifunctional treatment against sepsis[119]. Cell membrane-derived biomimetic nanoplatforms trap and neutralize toxins. Nano-delivery systems customize agent kinetics and enhance targeted distribution, reducing peripheral exposure and toxicity[120]. Clinical trials for sepsis treatment include amikacin-loaded lipid nanocrystals, Resatorvid emulsion, Pegylated filgrastim, Spi-Argent®, Arikayce®, and more[117]. Figure 2 outlines the various applications of nanoparticle technology in sepsis management [120].

Patient centered care

Several innovations have occurred in the 21st century towards a more patient-centered approach in ICU care, emphasizing communication, engagement, and individualized support for both patients and their families[121]. The primary focus is on 'Family-centered rounds', which involve including family members in daily rounds. It has enhanced communication, transparency, and shared decision-making between healthcare providers and the patient's family, fostering a collaborative care approach and improving outcomes[122]. Secondly, the 'Tele-ICU services' enable timely interventions, facilitate communication with off-site specialists, and provide an additional layer of support, particularly in

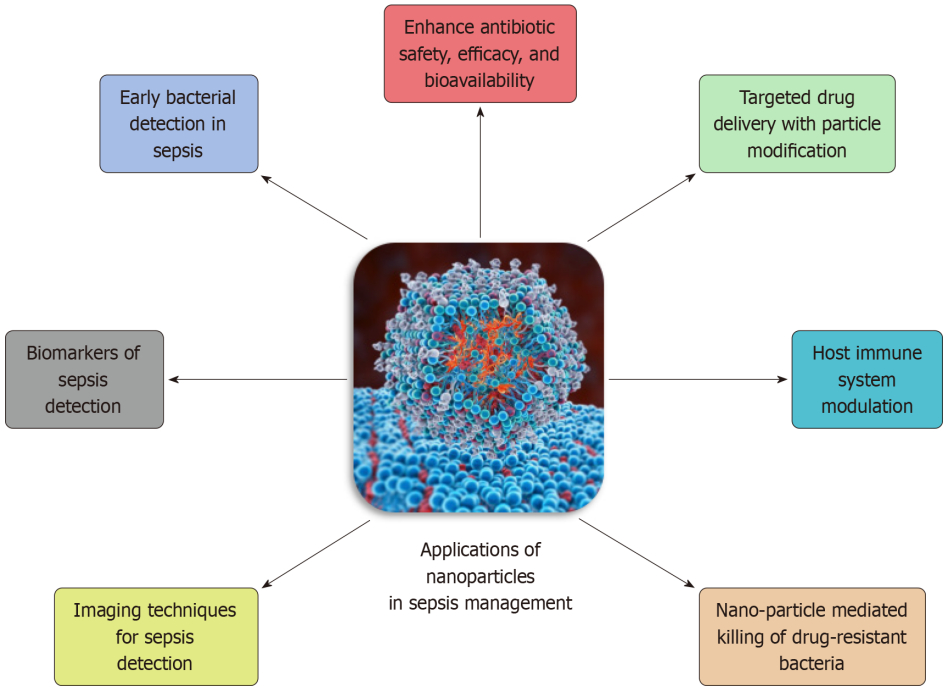

Figure 2 Applications of nanotechnology and nanoparticles in sepsis management (adapted from Zhou *et al*[120]).

underserved or rural areas or resource-limited countries[123].

Thirdly, the use of 'Patient and family education technologies' has empowered patients and their families with information about medical conditions, treatment options, and post-discharge care, promoting a more informed and engaged healthcare experience[124]. Additionally, 'Virtual visitation programs' have addressed challenges related to physical visitation, particularly during the COVID-19 pandemic, by allowing patients to connect with their loved ones virtually, positively influencing emotional well-being. Lastly, the 'Patient-controlled comfort measures' have integration of customizable environmental and comfort controls. This allows patients to personalize their immediate surroundings, influencing factors like lighting and noise levels, contributing to a more comfortable and healing-oriented environment including pain and sedation control[125].

CONCLUSION

In conclusion, the landscape of critical care medicine in the 21st century has been marked by remarkable advancements, underscoring a commitment to enhancing patient outcomes in ICUs. The summarized developments, ranging from precision medicine and telemedicine to AI and advanced life support systems, showcase the dynamic evolution of critical care practices. These innovations not only demonstrate a keen focus on individualized patient care but also reflect a broader integration of technology and research into clinical decision-making processes. The emphasis on infection control, ventilation strategies, and sepsis management underscores a commitment to combating emerging challenges in critical care.

Furthermore, the transformative shift towards patient-centered care highlights a holistic approach, recognizing the importance of addressing not only the medical needs but also the psychological and emotional well-being of patients. As the field continues to evolve, the promise of even more innovative solutions is on the horizon, poised to meet the complex and ever-evolving challenges of modern medicine in the critical care setting. These advancements collectively contribute to a future where the synergy of technology, research, and patient-centered approaches not only improves the quality of care but also saves lives in ICUs.

FOOTNOTES

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ORCID number: Smitesh Padte 0009-0006-0556-0316; Vikramaditya Samala Venkata 0000-0002-2046-2953; Priyal Mehta 0009-0004-4175-5327; Sawsan Tawfeeq 0009-0006-7849-5914; Rahul Kashyap 0000-0002-4383-3411; Salim Surani 0000-0001-7105-4266.

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P-Editor: Zheng XM

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MINIREVIEWS

Driving pressure in mechanical ventilation: A review

Syeda Farheen Zaidi, Asim Shaikh, Daniyal Aziz Khan, Salim Surani, Iqbal Ratnani

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Syeda Farheen Zaidi, Department of Medicine, Queen Mary University, London E1 4NS, United Kingdom

Asim Shaikh, Department of Medicine, Aga Khan University, Sindh, Karachi 74500, Pakistan

Daniyal Aziz Khan, Department of Medicine, Jinnah Postgraduate Medical Center, Sindh, Karachi 75510, Pakistan

Salim Surani, Department of Medicine and Pharmacology, Texas A and M University, College Station, TX 77843, United States

Iqbal Ratnani, Department of Anesthesiology and Critical Care, Houston Methodist Hospital, Houston, TX 77030, United States

Corresponding author: Salim Surani, FCCP, MD, Professor, Department of Medicine and Pharmacology, Texas A and M University, No. 40 Bizzell Street, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

Driving pressure (ΔP) is a core therapeutic component of mechanical ventilation (MV). Varying levels of ΔP have been employed during MV depending on the type of underlying pathology and severity of injury. However, ΔP levels have also been shown to closely impact hard endpoints such as mortality. Considering this, conducting an in-depth review of ΔP as a unique, outcome-impacting therapeutic modality is extremely important. There is a need to understand the subtleties involved in making sure ΔP levels are optimized to enhance outcomes and minimize harm. We performed this narrative review to further explore the various uses of ΔP, the different parameters that can affect its use, and how outcomes vary in different patient populations at different pressure levels. To better utilize ΔP in MV-requiring patients, additional large-scale clinical studies are needed.

Key Words: Driving pressure; Acute respiratory distress syndrome; Mortality; Positive end-expiratory pressure; Ventilator induced lung injury; Mechanical ventilation

Core Tip: Driving pressures (ΔP) of < 15 have demonstrated the greatest benefit in mortality. It is most utilized in patients with acute respiratory distress syndrome (ARDS). Some large-scale randomized controlled trials are currently underway; their results will dictate the outcomes of certain ΔPs under specialized conditions, such as the feasibility of reducing ΔP in ARDS patients on mechanical ventilation and the impact of lateral positioning on ΔP. It is clear, however, that careful implementation of ΔPs can greatly improve outcomes.

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INTRODUCTION

Driving pressure (ΔP) is a fundamental element in mechanical ventilation. Its primary function is to overcome the elastic forces of the pulmonary system. It is derived from the difference between end-inspiratory airway pressure, commonly known as the plateau pressure (Pplat), and positive end-expiratory pressure (PEEP) in the absence of spontaneous respiration[1-4].

ΔP is derived from the ventilator and serves as a function of respiratory compliance and tidal volume. It reflects the pressure difference within a singular breath and is one of the major parameters implicated in lung stress[5,6]. Recent studies have shown a plausible association between ΔP and improved survival in patients with acute respiratory distress syndrome (ARDS)[5,7-13]. Even though it is commonly used across critical care centers around the globe, it is a measure that requires further introspection to harness its predictive potential and guide safe and effective ventilation.

This review article discusses the dynamics of mechanical ventilation and explores the role of ΔP, its significance in recent studies, and the resulting implications for future research.

PHYSIOLOGY AND MECHANICS OF MECHANICAL VENTILATION

Mechanical ventilation allows gas exchange and attenuates increased work of breathing in the setting of an acute compromise of the respiratory system. The mechanics are expressed through indices such as pressure, flow, volume, resistance, work of breathing, and compliance, which directly influence lung volumes, functional residual capacity, and the resulting gas exchange[5].

Physiologically, the respiratory circuit works as a negative pressure system. On inspiration, the diaphragm is pushed down, and negative pleural cavity pressure is generated. A net negative pressure in the airway serves as a suction for air to be brought into the lungs. The negative pressure then, in turn, decreases the right atrial pressure and generates a similar suction effect in the inferior vena cava, which results in an increase in venous return[14].

During mechanical ventilation, however, this physiology is altered, and a positive pressure is transmitted into the pulmonary system instead. This leads to a more positive pressure in the pleural space and less of that suction effect. This positive pressure is also exerted on the right atrium, which leads to a decrease in venous return and preload. The net impact is a reduced cardiac output due to the underfilling of blood in the left heart and low mean arterial pressures[15]. An understanding of the effects of artificial ventilation is important to guide management in patients and adjust for the consequences.

The baby lung concept was coined by Gattinoni and Pesenti[16] after they observed computed tomography scans of patients with ARDS or acute lung injury. They noticed that the total aerated lung tissue of these patients held dimensions of 300-550 g, similar to a 5-6-year-old child. They proposed that the ARDS lung is not stiff but, in fact, functionally small-suggesting that the elasticity of the lung is most likely intact and that the lung tissue may change dimensions after recruitment maneuvers such as prone positioning. They highlighted that gentle lung treatment should thus be employed to avoid baro-volutrauma inflicted by standard aggressive resuscitative strategies. This theory has gained traction as further research on ARDS has supported their findings, and the discovery and application of ΔP in research has improved outcomes[17]. In general, a tailored approach to ventilation is required to match a patient's variable physiology to reduce the chances of ventilator-induced lung injury (VILI).

FACTORS THAT INFLUENCE THE MECHANICS OF ARTIFICIAL VENTILATION

Impedance

The forces that impede ventilation include non-elastic or respiratory system resistance, which occurs when gas flows within the airway circuit, and elastic resistance, which occurs in the absence of gas flow in the circuit[18]. Examples of non-elastic resistance include frictional resistance to gas flow, viscoelastic resistance from the deformation of thoracic tissues, and finally, the inertia of gas flow and tissue movement[18]. While small levels of impedance do not always mean

underventilation of lung tissues, higher levels of impedance require higher ΔPs for effective ventilation. These forms of resistance can be reflected in the equation: *(*Resistance R = Δ pressure/flow).

The elastic resistance comprises of resistance exerted by the chest wall and lung tissue, along with resistance exerted by the surface forces at the alveolar gas-liquid interface. The elastic resistance can be used to derive total compliance of the lung and the chest wall[18]. These forms of resistance can be represented by the following equations: (Compliance Crs = Δ volume/Δ pressure), [Elastance (EL) ELrs = Δ pressure/Δ volume = 1/C].

As a rule, high levels of compliance, and therefore lower levels of EL, allow for less effective mechanical ventilation at lower ΔPs. Hence, in certain conditions that alter these mechanics, such as in emphysema, which leads to higher compliance, increased levels of ΔP are required to maintain adequate levels of ventilation.

PRESSURE

Airway pressure

Airway pressure is equal to alveolar pressure in the resting state and depicts the pressure generated to overcome the retractive elastic forces of the pulmonary system. It is reflected in the following equation[19,20]; (airway pressure = flow x resistance + alveolar pressure).

Airway pressure dictates the ΔPs required for adequate ventilation in all patients. Higher alveolar pressures and general airway resistance require increasing levels of ΔP to maintain effective ventilation.

Pplat

Pplat is the pressure exerted by the ventilator into the alveoli and small airways of the lung. It is calculated during an inspiratory pause of 0.5-1 s on the ventilator when the respiratory muscles are relaxed. This pressure approximates the mean peak alveolar pressure[21,22]. As noted previously, resting high Pplats are incorporated in ΔP calculations in order to identify requirements for overcoming inside pressures.

Transpulmonary pressure

Transpulmonary pressure (P_{TP}) is the distending pressure of the lungs and is derived by calculating the difference between the pressure within the alveoli (P_{ALV}) and the pleural pressure (P_{PL})[23]. The transpulmonary pressure is described by the following formula: ($P_{TP} = P_{ALV} - P_{PL}$).

ΔP

ΔP is derived from the difference between Pplat and PEEP. It is essentially the pressure required to open the alveolar sacs. Since static lung compliance (Cstat) is derived from the formula; Tidal volume/(Pplat-PEEP), ΔP is derived as an inverse function of respiratory system compliance (C_{rs}). The higher the ΔP, the lower the compliance of the lung and, therefore, an increased risk of volutrauma. Henceforth, ΔP is the foundational pillar of mechanical ventilation. Adequate ΔP levels are needed for effective air delivery to overcome resistances, high inner pressures, and losses during ventilation. It is described by the following equations[24]: (ΔP = Pplat - PEEP), ($\Delta P = VT/C_{rs}$).

Transpulmonary ΔP

Transpulmonary ΔP (ΔP_{pL}) can be defined as the difference between the P_{TP} at end inspiration and end-expiration.

Peak pressure

Peak pressure is the maximum recorded pressure at the end of inspiration in the presence of airflow. Peak pressure is dependent on tidal volume, respiratory rate, and airflow[14,20].

Intrinsic PEEP

Intrinsic peak expiratory pressure reflects the pressure exerted by the residual volume in the lung due to incomplete exhalation. It can be calculated by doing an expiratory pause and measuring the end-expiratory pressure[14].

Stress

Lung stress refers to the pressure required to distend the lung against the counterforce exerted by the chest wall. Stress is depicted best by P_{TP}, which is the difference between airway pressure (Paw) and P_{PL}. Its formula is represented by ($Paw-P_{PL}$).

Despite its high predictability, P_{TP} is not frequently used due to the difficulty of calculation, and Pplat is thus used as an alternative. Pplat is reflective of alveolar pressure when the airflow is zero and is calculated during an inspiratory pause on the ventilator when the respiratory muscles are relaxed.

Strain

Lung strain is directly related to lung stress and refers to the change in lung volume when compared to its volume during regular respiration[20,23,25].

MODIFIABLE INPUTS IN ARTIFICIAL MECHANICAL VENTILATION

Tidal volume

Tidal volume is the amount of air exchanged during ventilation at rest and is matched by ideal body weight or approximations based on the patient's disposition[14]. Tidal volume follows a proportional relationship with ΔP in mechanical ventilation. Higher tidal volumes increase ΔPs. This can be modified as needed.

PEEP

PEEP or extrinsic PEEP is the end-expiration pressure that is delivered by mechanical ventilation to prevent the lung from collapsing. It is important to maintain the patency of the small airways and alveoli. This, in turn, increases lymphatic flow and allows adequate drainage of the lung. Therefore, lower levels of PEEP increase ΔPs.

Respiratory rate

The rate of ventilation is set to achieve target levels of carbon dioxide according to the patient's metabolic demands[14]. Respiratory rate is a component of mechanical power (MP) along with ΔP. These levels can be changed depending on ventilation requirements and desired MP metrics.

MEASURES OF PATIENT-MACHINE INTERACTION

Mechanical energy

Mechanical energy (EnergyL) refers to various forms of energy transferred after each ventilatory cycle and can be derived simply through Pplat (ΔPL) and the EL of the lung. It is described in the following formula(s): (EnergyL = ΔPL 2/EL), [(EnergyL = ΔV2 × [(0.5 × ERS + RR × (1 + I:E)/60 × I:E × Raw) + ΔV × PEEP)].

MP and intensity

MP refers to the EnergyL multiplied by the rate of respiration, thus reflecting the EnergyL transferred per minute from artificial ventilation. This value captures both static and dynamic metrics that influence respiration[26]. MP has recently emerged as a novel and promising predictor of VILI. While its incorporation clinically is yet to be widened, it has shown promise. Maintaining lower rates of MP by considering the dynamic metrics it incorporates, can reduce rates of VILI. The formula of MP is reflected as [*MP = (EnergyL x RR) or RR W=RR ∫0 VT PawdV∫*]

CLINICAL RELEVANCE OF ΔP

In recent years, the understanding behind VILI has rapidly expanded from a limited perspective of pressures, volumes, and tidal cycles to an understanding of forces and their interplay in periods of stress and strain while being subjected to different forms of energy and power. The value of ΔP has recently gained traction in research and practice due to key findings demonstrating the impact of high ΔPs, resulting in low compliance and increased risk of volutrauma. Ultimately lead to higher morbidity and mortality in patients requiring artificial ventilation-particularly in cases of ARDS.

A meta-analysis by Amato *et al*[3] analyzed 9 randomized controlled trials and demonstrated that in intensive care settings, ARDS patients with elevated ΔPs of 15 cm H_2O were positively associated with higher mortality (relative risk, 1.41; 95%CI: 1.31 to 1.51; $P < 0.001$), (relative risk, 1.36; 95%CI: 1.17 to 1.58; $P < 0.001$), after every 1 standard increment in ΔP (approximately 7 cm of water). This result was despite the protective range of tidal volumes and Pplat[3]. A ΔP less than 15 cm H_2O was considered to be a safe threshold to guide ventilation in ARDS patients and decrease mortality[3]. This study, despite its limitations, provided a significant understanding of the delicate role ΔPs can play in the management of ARDS and the intricate and precise difference the slightest of modifications can make.

In addition, the large observational cohort study to understand the global impact of Severe Acute Respiratory failure (LUNG-SAFE), a multicenter, international study, was conducted to identify the incidence of ARDS in intensive care units but also to collect information about the associated ventilatory management, therapies, and outcomes. The multivariate analyses concluded that high peak pressures, higher Pplats, high ΔPs of > 14 cm H_2O, and low PEEP were associated with increased mortality in these patients[27].

This notion gained additional strength when Bellani *et al*[28], in their retrospective study, also demonstrated that a higher ΔP was associated with higher mortality rates. Chiumello *et al*[2] revealed that ARDS patients with higher than threshold values of ΔP experienced lung stress and thus were likely to experience more ventilator-associated lung injury due to cyclic stretch. It can, therefore, be inferred that the ΔP reflects the stress on the lungs and that outputs like tidal volumes should be adjusted for ΔP instead of traditional measures. Similarly, PEEP can be adjusted to accommodate the loss of airway recruitment, increased levels of stress and strain, and the resulting increase in ΔP. A higher PEEP will improve lung compliance and attenuate the high ΔPs resulting from lung inhomogeneity[29,30].

Villar *et al*[31] provided evidence that ΔP was related to an increase in hospital mortality despite optimized protective ventilation. In addition, Urner *et al*[32] assessed the dose-effect relationship between ΔP and survival. A hazard ratio of 1.064 (95%CI 1.057-1.071) was seen with a daily increment of ΔP. A higher mortality was noted with ΔP levels of ≥ 15 cm H_2O, even if present for brief period. Furthermore, a higher ΔP level had a greater increase in mortality when compared

to PaO_2/FiO_2 or other metrics of oxygenation.

While it has emerged as a promising metric to help attenuate events of VILI, despite reliable estimation of lung pressures, ΔP alone may not provide an accurate measure of risk. The process of VILI occurs due to a complex interplay of various forces, therefore multiple parameters need to be accounted for and addressed when managing mechanical ventilation in these cases.

MONITORING, MEASUREMENT, AND PATIENT CHARACTERISTICS

ΔP is measured in two ways. Firstly, in the setting of an absence of spontaneous breathing, an end-inspiratory hold of a few seconds on the ventilator provides the value of Pplat. The ΔP can be derived from the following formula (Pplat-PEEP). This method can be vulnerable to oversimplification and bias when auto-PEEP is significant and not accounted for. It can also be erroneous when clinical leaks such as bronchopleural fistulas or micro leaks are found in the apparatus or tubing. These errors can result in second-by-second variability in Pplat values. A way to counter this discrepancy is to shift the ventilator to volume control mode and set a shorter inspiratory pause of 0.3 s. This method will provide consistent measures of Pplat and thus more reliability due to shorter occlusion periods[33].

Foti *et al*[34] described the method of calculating ΔP in static conditions with pressure support ventilation. The derivation of Pplat is performed after an end-inspiratory hold and respiratory muscle relaxation [when the pressure generated by the ventilator (Paw) reaches a plateau] This method was proven by Akoumianaki *et al*[35] to overestimate Pplat and ΔP due to confounding by expiratory muscle activity. Another potential problem that distorts an accurate read of the Pplat is reverse triggering, wherein a patient initiates inspiratory effort during the middle or end of a passive inspiration by the ventilator. This is a form of ventilator desynchrony that tends to occur when a patient is weaning off sedation or paralysis. This results in an underestimation of Pplat due to a misleading drop in end-inspiratory pressures [36].

Therefore, in the case of spontaneous breathing, the derivation of ΔP becomes slightly more complex, as the patient component of respiratory effort needs to be accounted for, which is essentially driving the breath. Therefore, the pressure applied by the ventilator (Pplat-PEEP) needs to be added to the pressure generated by the respiratory muscles; *i.e.*, P_{PL}. The P_{PL} can be accurately estimated through esophageal manometry, and this dynamic measurement is called the PL swing. The swing describes the ΔP for insufflation of the lung and generation of flow representing the overall change in P_{PL}[37]. Therefore, during spontaneous breathing, the formula of ΔP changes to the following: $\Delta P = (Pplat\text{-}PEEP + \Delta P_{PL})$.

Another important value Bertoni *et al*[38] investigated was the ΔPocc (occluded inspiratory airway pressure), also known as the Pes swing. This value emerged from performing an expiratory hold to ascertain the patient's inspiratory effort. The deflection depicts the change in P_{PL}. This was described as dynamic P_{PL}. The equation to describe dynamic P_{PL} is: *Predicted dynamic* $P_{PL} = [\Delta P_{Ldyn} - (Ppeak - PEEP) - 0.66 \times \Delta Pocc]$. In addition to this, Telias *et al*[39] also showed the value of the airway occlusion pressure (P0.1) metric that is measured in the first 100 ms. of an occlusion. This metric was used to accurately detect inspiratory effort and low ventilatory drive. P0.1 can also be used to ascertain high values of dynamic.

ΔP IN SPECIAL POPULATIONS

ARDS

In ARDS, the lung becomes less compliant, resulting in a reduced proportion of recruitable tissue that can be ventilated. This was best illustrated by the previously described baby lung concept[16]. These alterations thus require modulation of ventilatory techniques to account for the loss of lung volume, such as adjusting tidal volume with compliance and increasing PEEP to target ΔP[3]. As discussed earlier, many studies have described the role of ΔP in patients with ARDS. The strong association of cyclical stretch and lung stress correlates with ΔP and overall survival in ARDS.

Blondonnet *et al*[40] analyzed ΔP at baseline and at 24 h in patients who had developed ARDS. The analysis showed that both baseline ΔP and respiratory rate were significantly lower. ΔP greater than 16.5 cm H_2O was predictive for ARDS development and vice versa. Similarly, Haudebourg *et al*[11] demonstrated that ΔP-targeted ventilation in patients with moderate to severe ARDS improved ventilatory parameters such as increased tidal volumes, lower MP requirement, and reduced respiratory rate. In addition, Guérin *et al*[7], in their study, showed that ΔP was more strongly associated with survival as compared to PEEP and tidal volume in ARDS patients. While many studies have highlighted the role of ΔP and its influence on outcomes, some studies suggest otherwise.

One such study by Romano *et al*[41] compared limiting ΔP with standard lung protective measures during ventilation of patients with ARDS. The tidal volume was set according to ideal weight; 4-8 mL/kg and a ΔP of 10 or the lowest possible was applied. The comparison group was ventilated according to the ARDSNet protocol with adjustments made in tidal volume based on Pplat. It was seen that both the ΔP and tidal volumes were lower in the ΔP-limited group as opposed to the conventional group, although there was no effect on outcomes.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO), an external circuit to directly oxygenate the blood and remove carbon dioxide, was unveiled in the 1970s, but its use took off in more recent years, increasing to a whopping 433% since 2006 [42]. ECMO is used to rest the lungs and decrease stress, strain, and intensity experienced in mechanical ventilation. It provides cardiac, respiratory, or cardiorespiratory support when needed. Ultra-low tidal volumes are employed, and

various strategies are used to achieve this. Current guidelines for mechanical ventilation with ECMO, target Pplat and tidal volumes corrected for ideal body weight[43].

A study by Gupta *et al*[44] analyzed ΔPs pre- and post-ECMO initiation to compare how high and low ΔPs influence mortality and outcomes. In this study, 46% of patients had increased ΔPs and higher drops in PEEP post-ECMO initiation. The study also showed a significantly longer length of ECMO stay in patients, perhaps due to poor parameters influencing clinician decision of weaning. High ΔP in ECMO was seen as a strong predictor of 30-d mortality in both adjusted and unadjusted analyses of patients receiving ECMO in both groups.

Magunia *et al*[45] showed in their study of patients receiving VV-ECMO that survivors had increased compliance levels and lower ΔPs as compared to non-survivors. Similarly, Chiu *et al*, in their study of patients with severe ARDS on ECMO, showed that the cut-off point between survivors and non-survivors was a 33% change in ΔP within the first 12 h with a sensitivity of 78% and a specificity of 67.9%[46].

In the study by Del Sorbo *et al*[47], the effects of changing ΔP were correlated with various variables. A linear relationship was demonstrated between the change in ΔP and the concentration of certain inflammatory mediators that correlate with VILI in lung epithelial cells. This finding suggests a strong predictive potential for VILI if ΔP is utilized adequately in these patients.

Surgical

In the surgical setting, there is a high likelihood of pulmonary complications, particularly in thoracic surgery, due to direct injury of lung tissues and open ventilation of one lung. This results in a heightened immune response and increased pulmonary vascular permeability, resulting in ARDS[48].

Blank *et al*[49] analyzed the ΔP and tidal volumes of patients undergoing thoracic surgery with two or one-lung ventilation and found that ΔP was a risk factor for overall postoperative morbidity with an odds ratio of 1.034 (97.5%CI. 1.001 to 1.068). In a meta-analysis of surgical patients, Neto and colleagues demonstrated a positive correlation between postoperative respiratory complications in patients with higher ΔPs with an odds ratio of 1.16 for each 1 cm H_2O increase in ΔP. No significant associations were found with tidal volume, and PEEP was only influential if it altered the ΔP[50].

In a cohort study conducted by Mathis *et al*[51] of cardiac patients undergoing surgery, modified ΔP was independently associated with decreased pulmonary complications. However, it was not clear whether active control of ΔP would result in improved outcomes, and the method of controlling or reducing ΔP was not particularly defined in their study.

Park *et al*[52] randomized patients who were receiving elective thoracic surgery into two ventilatory groups. One group was ventilated with standard measures of low tidal volumes, a peep of 5 cm H_2O, and tailored maneuvers to increase recruitment were utilized as needed. Low tidal volumes were used in the second group, but PEEP was titrated according to the desired ΔP. Postoperative pulmonary complications were higher in the first conventional group (12.2%) as compared to the second group, where ΔP was titrated (5.5%). The incidence of ARDS was also elevated in the first group (5 patients) as opposed to the second group (0 patients). Despite the impressive findings, there was no impact on the development of ARDS by day 7, nor was there any decrease in the length of intensive care unit (ICU) and hospital stay.

COPD

In the setting of chronic obstructive pulmonary disease, there is increased air trapping, obstruction, and elevated airway resistance. This leads to an increase in end-expiratory lung volume and an increase in end-expiratory alveolar pressure-also referred to as intrinsic peep. It is thus necessary to utilize an end-expiratory and inspiratory hold to accurately generate compliance and therefore ΔP[53]. Although specific studies on COPD patients and the role of ΔP in their ventilation have not been captured, COPD patients require monitoring to ensure the emptying of lung air and thus, PEEP is primarily adjusted.

Obesity

Obese patients typically have higher chest wall EL, low or more negative P_{TPs}, and lower compliance. Due to the variability of these values, a true reflection of ΔP cannot be obtained accurately. In obese patients, transpulmonary ΔP is more reliable, but more studies are required to better explain these assumptions[54]. De Jong *et al*[55] studied the relationship between ΔP during the first day of ventilation and 90-d mortality in 100 obese patients and 262 non-obese patients with ARDS but found no association between ΔP and mortality in obese patients. A limitation of the study was the reliance on body mass index as a measure of obesity and body fat percentage was not accounted for.

Pregnancy

In pregnancy, the physiology of the respiratory symptom is altered. Due to the chemical effects of progesterone and prostaglandins E1 and E2, bronchodilation occurs. Prostaglandin F2alpha, however, can increase airway resistance and constrict bronchial smooth muscles. In addition, due to uterine distension, the diaphragm is elevated, and there is an increase in end-expiratory abdominal pressure (Pga). The P_{PL} also increases, leading to a reduction in expiratory residual volume (ERV) and functional residual capacity (FRC) due to early closure of small airways. The chest height also becomes shorter and ERV is 8%-40% lower during the second half of pregnancy. The tidal volume and occlusion pressure also increase, reflecting a need for adjustment for ventilation[56,57].

Respiratory failure in pregnancy is rare, occurring in 1 in 10000 pregnancies, but its incidence has increased, particularly since coronavirus disease 2019 (COVID-19)[58]. A study by Vasquez *et al*[59] showed that respiratory mechanics in pregnant females remained similar to the general population that required ventilation in cases of COVID. In a study by

Lapinsky *et al*[60], they conducted a retrospective analysis of the impact of COVID-19 on mechanical ventilation parameters. In the case of ΔPs, survivors had an average of < 14 cm H_2O, and non-survivors had higher ΔPs. Post-delivery, there was an increase in the PaO_2/FiO_2 ratio, but there was no change in static compliance or ΔP.

Pediatric

The first pediatric study to assess ΔP in mechanically ventilated children was conducted by Schelven *et al*[13] In their study, they demonstrated higher disease severity, MV indication, and an increase in extubation time in patients with higher ΔP[1]. Similarly, a retrospective study by Rauf *et al*[9] assessed the effects of ΔP on morbidity and mortality in children admitted to the ICU with ARDS. The study divided the children into two groups; one with ΔP of 15 cm H_2O in the first hour and the other with lower than 15 cm H_2O ΔP. It was seen that children with lower pressures had significantly lower morbidity in ARDS. A study by Yehya *et al*[61], however, suggested that ΔP in children with ARDS was not an independent predictor of mortality. It is worth noting that ΔP was not accurately defined in either of these studies.

Elderly

Aging can result in an alteration of lung physiology through increased pro-inflammatory and fibrotic factors. Decreased chest wall compliance and higher levels of air trapping are noted due to the loss of lung tissue, which ultimately leads to a reduction in FEV1[62]. No study has specifically explored the effects of aging on ΔP. Theoretically, it is assumed that it would increase ΔP due to the change in compliance. It is clear that elderly patients are far more susceptible to higher morbidity and mortality in the ICU setting, and several studies have reported age as a strong predictor for mortality[63-66].

Heart failure

Cardiac failure due to structural and functional causes frequently results in pulmonary edema, which requires mechanical ventilation strategies. In a fluid-filled lung, the lung's compliance dramatically decreases, and the resistive forces increase. The lung behaves in a similar way to ARDS due to the pulmonary edema and, therefore, holds the same pathological changes in mechanics.

In an observational study by Yang *et al*[67], they analyzed 632 patients with heart failure who required invasive ventilation. It was found that higher ΔPs above a threshold of 14.27 cm H_2O were found to be independently associated with increased in-hospital mortality if patients were ventilated over 48 h. With each increment of 1 cm H_2O of ΔP, an increased odds ratio of 1.12 in the risk of in-hospital mortality was observed. In contrast, Schmid *et al*'s study showed that there was no association with mortality in non-ARDS patients, including patients with heart failure and other cardiac-related diseases[10]. A summary of the cumulative findings of ΔP in special populations is shown in Table 1.

CLINICAL OUTCOMES

A cohort study by Goodwin *et al*[68] examined electronic health records to ascertain the importance of ΔP and EL in influencing clinical outcomes. The study assessed various factors in 2334 homogenous patients with respiratory failure in the ICU. After adjustment for covariates, exposure to ΔPs > 15 cm H_2O was associated with a 19% increased risk (1.19; CI 1.07-1.33) of mortality and 1.5 fewer ventilator-free days as compared to controls. Increased respiratory EL of > 2 cm H_2O/mL/kg was also associated with a 13% increase in the risk of mortality without any impact on the length of stay or ventilatory-free days. This study established a time-weighted averaging method to derive exposure of ΔP and other metrics to give a consistent reading of ΔP and its resulting influence[2].

ΔP and EL have been shown by numerous studies as predictors of reduced lung function, increased stress, and a high likelihood of VILI. Employing LUNG-SAFE ventilation strategies has expanded from lowering tidal volume to acceptable thresholds of plateau ΔPs and reducing ventilation frequency. Currently, values of Pplat of 30 cm H_2O and ΔP of 15 cm H_2O are considered the upper limit. Intervention is thus necessary to tailor ventilatory care[69-71].

FUTURE DIRECTIONS AND LATEST RESEARCH

Many studies have provided significant insight into the relevance of ΔP as a detrimental factor in guiding ventilation. These studies have demonstrated this by showcasing high numbers of adverse events in the setting of elevated ΔP. It is worth noting that these studies are not without limitations, with many of them lacking causality. Therefore, there is a need for more comparative analyses to better predict the validity of ΔP when compared to other parameters such as PEEP, EL, tidal volume, MP, *etc.* A standardized method of quantifying ΔP is also crucial to ensure accuracy, and a protocol should be introduced for clinicians to follow if they plan to conduct further research on the impact of ΔP. The adjunct of additional modalities, such as Electrical Impedance Tomography (EIT) and Ultrasound, will further improve validity and give valuable insight[27]. ΔP in ECMO should also be utilized and studied to extract valuable findings.

It is common in studies to derive ΔPs during passive ventilation, but efforts should be made to explore ΔPs in the presence of spontaneous breathing. This will deliver additional comparative data and assess whether there are any shifts in ΔP while revealing additional metrics that may directly or indirectly influence results. The newer generation of ventilators should also be introduced when feasible-to guide clinicians in accounting for all the dynamic and static forces

Table 1 Findings from clinical studies regarding driving pressure

Population	Ref.	Study design	Sample	Findings
ARDS	Blondonnet *et al*[40]	Prospective cohort; secondary analysis	221 patients with at least 1 risk factor for ARDS	15% developed ARDS within 7 d who had higher baseline ΔP
ARDS	Guerin *et al*[7]	2 randomized controlled trials	787 patients	DP was more strongly associated with survival as compared to PEEP and tidal volume in ARDS patients
		Secondary analysis		PEEP and Tidal volume were not associated with death in any model
ARDS	Romano *et al* [41]	Pilot randomized, controlled, nonblinded trial	31 patients with ARDS on invasive mechanical ventilation with a driving pressure of ≥ 13 cm H_2O	DP and tidal volumes were lower in the driving pressure-limited group as opposed to the conventional group, although there was no effect on outcomes
ARDS	Chiumello *et al*[2]	Prospective cohort	150 patients	At ICU admission, non-surviving patients had a higher arterial carbon dioxide compared to survivors; The transpulmonary driving pressure was significantly related to the airway DP; The transpulmonary driving pressure was significantly related to lung stress
ARDS	Amato *et al*[3]	Meta-analysis of 9 RCTs	3562 patients in the ICU	ARDS patients with elevated DP of 15cm H_2O were positively associated with higher mortality; A DP of less than 15 cm H_2O was a safe threshold to guide ventilation in ARDS patients and decrease mortality
ARDS	Bellani *et al* [27]	Prospective cohort	459 ICUs; 12906 patients	High peak pressures, higher plateau pressures, high driving pressures of > 14 cm H_2O, and low peep were associated with increased mortality; There was a direct relationship between both plateau and DP and mortality
ARDS	Bellani *et al* [29]	Retrospective cohort study	154 patients	DP was higher, compliance was lower and peak pressure was similar, in non-survivors versus survivors; Lower respiratory system compliance and higher driving pressure were each independently associated with an increased risk of death
ARDS	Urner *et al*[32]	Registry-based cohort study	9 ICUs; 12865 patients requiring > 24 h of mechanical ventilation	Mortality was 18.1% with DP < 15 cm H_2O compared with 20.1% under usual care
ARDS	Haudebourg *et al*[11]	Prospective cohort	51 adult patients	The change from PBW to ΔP-guided ventilation was thus accompanied by an overall increase in tidal volume from 6.1 mL/kg PBW to 7.7 mL/kg PBW (6.2-8.7), while the respiratory rate was decreased from 29 breaths/min to 21 breaths/min
ECMO	Gupta *et al* [44]	Retrospective cohort	192 patients	47% had a decrease in DP, whereas 32 46% had an increase in DP, and 7% had no change in DP after ECMO initiation. Those with an increase in DP had a significantly longer stay on ECMO than those without; Higher DP 24 h after ECMO initiation was associated with an increase in 30-d mortality
ARDS	Del Sorbo *et al* [47]	Randomized crossover physiologic study	10 patients	A linear relationship was seen between the change in driving pressure and the concentration of IL-6
ECMO	Magunia *et al* [45]	Retrospective cohort	105 patients undergoing VV-ECMO	ΔP was greater than 15 mbar in non-survivors
ECMO and ARDS	Chiu *et al*[46]	Retrospective cohort	158 patients with severe ARDS on ECMO	After ECMO initiation, non-survivors had significantly higher dynamic DP until day 7 than survivors; Acute Physiology and Chronic Health Evaluation II score, ARDS duration before ECMO and mean driving pressure were independently associated with mortality
Surgical	Blank *et al*[49]	Retrospective cohort	1019 patients undergoing thoracic surgery with ventilation	DP was a risk factor for overall post-operative morbidity
Surgical	Neto *et al*[50]	Meta-analysis	17 randomized controlled trials, including 2250 post-operative patients	DP was associated with the development of postoperative pulmonary complications; An increase in the level of PEEP that resulted in an increase in DP was associated with more postoperative pulmonary complications
Surgical	Mathis *et al* [51]	Observational Cohort	4694 patients	10.9% experienced pulmonary complications
Surgical	Park *et al*[52]	Double-blind, randomized, controlled trial	292 patients	Melbourne Group Scale of at least 4 occurred in 8 of 145 patients in the DP group
	Li *et al*[71]	Systematic review	640 patients	The incidence of PPCS was lower and the compliance of the

		and meta-analysis		respiratory system was higher in the DP-oriented group during OLV
Obesity	De Jong *et al* [55]	Retrospective cohort	72% non-obese and 28% obese patients	The mortality rate at day 90 was 47% in the non-obese and 46% in the obese patients; In obese patients, driving pressure at day 1 was not significantly different
Pregnant	Lapinsky *et al* [60]	Prospective cohort	In 21 ICUs 69 patients requiring invasive mechanical ventilation, and 47 patients delivered while on the ventilator	Survivors had an average DP of < 14 cm H_2O; Maternal mortality rate of 17.5 %, and perinatal mortality rate of 15.4%; The mortality rate was lower than in the general COVID-19 population
Pediatric	Rauf *et al*[9]	Retrospective cohort study	380 children in the ICU	Children in the group with low ΔP (< 15 cm H_2O) had significantly lower median duration of ventilation, length of stay and ventilator-free days
ARDS	Yehya *et al* [61]	Prospective cohort study	544 children	DP was not an independent predictor of mortality
Pediatric	Schelven *et al* [13]	Prospective cohort study (secondary analysis)	222 children	Higher disease severity, MV indication, and increase in extubation time in patients with higher DPs
Heart Failure	Yang *et al*[67]	Retrospective cohort	632 patients	DP was independently associated with in-hospital mortality
No ARDS	Schmidt *et al* [10]	Retrospective cohort	622 patients	ΔP was not independently associated with hospital mortality

ARDS: Acute respiratory distress syndrome; PEEP: Positive end expiratory pressure; ICU: Intensive care unit; ΔP: Change in pressure; MV: Mechanical ventilation; DP: Driving pressure; OLV: One-lung ventilation; PPCS: Postoperative pulmonary complications; ECMO: Extracorporeal membrane oxygenation; PBW: Predicted body weight; COVID-19: Coronavirus disease 2019; RCT: Randomised controlled trials.

at play so that they can determine attributable risk. Further research on ARDS can benefit from using measurements such as esophageal manometry, as transpulmonary ΔP is a more accurate representation of the force being applied to the lung. An effort should be made to conduct more studies that include different pathologic states that lead to ARDS and clarify any variations in ΔP and ventilatory parameters.

In addition, more randomized controlled trials are needed to better understand the usefulness of ΔP in practice, establish causality, and determine its impact on long- and short-term outcomes. Further exploration of the impact of ΔP in various subsets of populations with varying etiologies is also needed. Basic science and physiological studies assessing the variability of pressures, lung volumes, oxygenation, and deformation of respiratory cells are needed to gain a more causal, sophisticated glance into cellular stress and strain[5].

Some up-and-coming trials that may provide further insight into the prospects and usefulness of ΔP were researched. Upon searching the term 'ΔP' in clinicaltrials.gov, many promising studies emerged that aim to elaborate on the role of ΔP in various situations. A few of them are described as follows.

ΔP limited ventilation for Patients With ARDS [ART-2-Trial ID: NCT02365038]; a multicenter pilot randomized control trial that is assessing the feasibility of limiting ΔP during ventilation of ARDS patients in one arm and employing the standard ventilatory guidance by ARDS Network strategy in the control arm. The tidal volume will be adjusted 3-8 mL/kg PBW to get target values of 13 cm H_2O in ΔPs calculated day 1 and day 3 of randomization.

Mechanical ventilation based on ΔP in lateral position (Trial ID: NCT04455789) A randomized, controlled, double-blind study of 60 patients undergoing total hip replacement surgery. The aim is to investigate the effects of different positions on ventilation utilizing traditional lung protective parameters in the control arm and a low ΔP arm. They aim to assess hemodynamic and respiratory values and overall postoperative outcomes.

ΔP during general anesthesia for open abdominal surgery (Trial ID: NCT03884543). A randomized multicenter double-blinded control trial to assess whether the application of high peep during mechanical ventilation to maintain low levels of ΔP helps prevent complications compared to standard low peep strategies. The study targets patients undergoing abdominal surgery who are at intermediate to high risk of pulmonary complications based on the ARISCAT score. These studies and many others hold strong promise in showing an appropriate application of ΔP and its impact in various settings.

CONCLUSION

ΔP has proven to be a highly significant metric when ventilating patients, particularly in ARDS. Adjusting for ΔP has shown improved clinical outcomes and fewer incidences of VILI. Considerations should be made to improve the accuracy of measurements and monitoring. Ongoing research should enhance our understanding of ΔP and how to best harness its potential in providing tailored, safe, and effective ventilation[3,4].

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Syeda Farheen Zaidi 0000-0002-3117-536X; Asim Shaikh 0000-0001-6984-9465; Daniyal Aziz Khan 0009-0003-4893-5605; Salim Surani 0000-0001-7105-4266; Iqbal Ratnani 0000-0002-1168-3041.

Corresponding Author's Membership in Professional Societies: Society of Critical Care Medicine.

S-Editor: Qu XL
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MINIREVIEWS

Inhaled volatile anesthetics in the intensive care unit

Erin D Wieruszewski, Mariam ElSaban, Patrick M Wieruszewski, Nathan J Smischney

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Erin D Wieruszewski, Patrick M Wieruszewski, Department of Pharmacy, Mayo Clinic, Rochester, MN 55905, United States

Mariam ElSaban, Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Nathan J Smischney, Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan J Smischney, MD, MS, Associate Professor, Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

Abstract

The discovery and utilization of volatile anesthetics has significantly transformed surgical practices since their inception in the mid-19th century. Recently, a paradigm shift is observed as volatile anesthetics extend beyond traditional confines of the operating theatres, finding diverse applications in intensive care settings. In the dynamic landscape of intensive care, volatile anesthetics emerge as a promising avenue for addressing complex sedation requirements, managing refractory lung pathologies including acute respiratory distress syndrome and status asthmaticus, conditions of high sedative requirements including burns, high opioid or alcohol use and neurological conditions such as status epilepticus. Volatile anesthetics can be administered through either inhaled route *via* anesthetic machines/devices or through extracorporeal membrane oxygenation circuitry, providing intensivists with multiple options to tailor therapy. Furthermore, their unique pharmacokinetic profiles render them titratable and empower clinicians to individualize management with heightened accuracy, mitigating risks associated with conventional sedation modalities. Despite the amounting enthusiasm for the use of these therapies, barriers to widespread utilization include expanding equipment availability, staff familiarity and training of safe use. This article delves into the realm of applying inhaled volatile anesthetics in the intensive care unit through discussing their pharmacology, administration considerations in intensive care settings, complication considerations, and listing indications and evidence of the use of volatile anesthetics in the critically ill patient population.

Key Words: Anesthesia; Critical care; Mechanical ventilation; Sedation; Volatile anesthetics; Sedative

Core Tip: This paper sets to explore the transformative impact of volatile anesthetics on surgical practices and their expanding role into intensive care settings. In this paradigm shift, volatile anesthetics prove a promising therapy modality with diverse applications in the critically ill patient population. From addressing intricate sedation needs to managing refractory seizure conditions, volatile anesthetics are a useful addition to intensivists' toolkits.

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INTRODUCTION

The discovery and application of volatile anesthetics has revolutionized surgical practices, with some of the earliest applications dating back to the mid-19th century when ether and chloroform were first utilized[1,2]. Since then, the use of inhaled anesthetics has evolved to be a fundamental component of anesthetic applications worldwide. Traditionally confined to the realm of operating theatres, volatile anesthetics are starting to carve niche uses among intensive care practices (Table 1).

In the dynamic landscape of intensive care, the utilization of volatile anesthetics is emerging as a promising avenue for various applications. These include addressing complex sedation requirements, managing refractory lung pathologies such as acute respiratory distress syndrome (ARDS) and status asthmaticus, employing them in conjunction with mechanical circulatory support, and managing neurological pathologies like status epilepticus (Table 2)[3-7]. The unique pharmacokinetic profiles of volatile anesthetics, characterized by rapid onset and offset, make them particularly well-suited for the intricate balance required in intensive care units[8]. Furthermore, their ability to achieve precise titration empowers clinicians to tailor management with heightened precision and thereby mitigating the risks associated with traditional modalities of sedation such as benzodiazepines[9,10].

This paper delves into the application of inhaled volatile anesthetics in intensive care units (ICUs) by exploring their pharmacological characteristics, administration modalities, listing various applications, and providing a comprehensive review of the evidence and potential future advances in this field.

PHARMACOLOGY

Over a century ago, scientists proposed the Meyer-Overton rule, which states that the potency of an anesthetic is linearly correlated to its oil/water partition coefficient. The downstream or indirect effects of this theory postulate that volatile anesthetics disrupt the lipid bilayer of cell membranes, according to their potency, thereby inducing conformational changes to proteins in the membrane resulting in its anesthetic effect. However, numerous examples (short chain 1-alkanols, perfluorinated alkanes, perfluoroalkyl methanols) have been described that seem to contradict this theory, suggesting alternative mechanisms by which volatile anesthetics exert their effect. Although data are sparse, some theorize that volatile anesthetics bind to specific ligand-gated ion channels within the cell membrane exerting a more direct effect. Others theorize that the anesthetic effects of volatile anesthetics are the result of disrupted lateral stresses in the lipid bilayer (lateral pressure profile) that are mechanistically linked to altered protein conformational equilibria[11]. Given the aforementioned evidence and admitting a degree of uncertainty, in general, volatile anesthetics appear to exert their effects through the central nervous system by augmenting signals to chloride and potassium channels through γ-Aminobutyric acid (GABA) receptors, and attenuating excitatory neurotransmission pathways through glutamate, acetylcholine, nicotinic, serotonin, and N-methyl-D-aspartic acid (NMDA) receptors (Figure 1)[12].

ADMINISTRATION CONSIDERATIONS

Delivery devices (intensive care unit only)

In general, there are two main methods of delivery of volatile anesthetics to ICU patients. One option includes the use of an anesthesia machine that allows for similar ventilator modes of ICU ventilators yet allows for rebreathing and scavenging of volatile anesthetics. Case reports have described the use of anesthesia machines used in the operating theatre that have been transported to the ICU for administration of volatile anesthesia in patients with acute respiratory failure such as from status asthmaticus[13,14].

Table 1 Pharmacology and overview of halogenated volatile anesthetics[8,78-81]

	MAC (%)	Blood:Gas at 37°C	Boiling point (°C)	Odor	Metabolism (%)	Cardiovascular effects	Central nervous system effects
Halothane	0.75	2.4	122	Organic solvent	15-20	Decrease CO, decrease HR	Decrease CPP, increase CBF
Isoflurane	1.15	1.4	48	Ethereal/pungent	0.2	Decrease CO, increase HR, decrease SVR	Decrease CPP, increase CBF
Desflurane	6.0	0.4	23	Ethereal/pungent	0.02	Increase HR, decrease SVR	Decrease CPP, increase CBF
Sevoflurane	2.0	0.68	59	Organic solvent	5	Decrease SVR	Decrease CPP, increase CBF. Can induce epileptiform EEG

CBF: Cerebral blood flow; CO: Cardiac output; CPP: Cerebral perfusion pressure; EEG: Electroencephalogram; HR: Heart rate; MAC: Minimum alveolar concentration; SVR: Systemic vascular resistance.

Table 2 Indications, advantages, and disadvantages of volatile anesthetics in the intensive care unit

Indication	Agents studied	Advantages	Disadvantages
Short-term postoperative	Desflurane, isoflurane, sevoflurane	Quick awakening; Faster extubation; Titratability; Minimal drug interactions; Minimal metabolism; Provides analgesia	No benefit on ICU length of stay; Reduces blood pressure
Prolonged sedation during mechanical ventilation	Isoflurane, sevoflurane	Faster return to spontaneous breathing; Titratability; Minimal drug interactions; Minimal metabolism; Provides analgesia	Special equipment required in ICU; Reduces blood pressure
Status asthmaticus	Isoflurane, sevoflurane	Bronchodilation	Reduces blood pressure
Status epilepticus	Isoflurane, desflurane	Sustained EEG burst suppression	May increase intracranial pressure through cerebral vasodilation
ARDS	Isoflurane, sevoflurane	Lung protective; Anti-inflammatory	Special equipment required in ICU; Reduces blood pressure
COVID-19	Isoflurane, sevoflurane	Decreased sedative, NMBA requirements	Special equipment required in ICU; Reduces blood pressure
Other high sedative requirements (burn, alcohol or opioid use at baseline)	Isoflurane, sevoflurane	Decreased inflammation in burns; Decreased sedative requirements	Not proven in literature, hypothesis generating at this time

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus infectious disease 2019; EEG: Electroencephalogram; ICU: Intensive care unit; NMBA: Neuromuscular blocking agent.

The second option is to use a device, such as the Anesthesia Conserving Device (AnaConDa), placed at the y-connector of the breathing circuit that allows for heated humidification, vaporization of anesthetic, and reflection of volatile gas to allow for rebreathing, minimizing the total requirement overall[15]. This system requires a medication pump to administer the liquid anesthetic, a gas scavenging system attached to the ICU ventilator, and a gas monitor to measure the end-tidal concentration of volatile anesthetic. The MIRUS™ (TIM, Koblenz, Germany) device is a newer system that also uses a reflector and allows administration of isoflurane and sevoflurane, but unlike the AnaConDa, it also allows for administration of desflurane[16]. Additionally, the MIRUS™ system also has a feature for adaptive regulation of end-tidal anesthetic concentration.

Delivery through extracorporeal membrane oxygenation membrane

Extracorporeal membrane oxygenation (ECMO) is a form of temporary life supportive therapy that provides a bridge to recovery, transplantation, or durable ventricular support in patients with medically refractory cardiac and/or respiratory failure. There is evolving evidence supporting a so-called 'awake ECMO' wherein sedation is minimized, allowing for participation in physical rehabilitation to promote recovery, particularly in the pre-transplantation setting[17]. However, sedation may still be necessary to facilitate safe ECMO flow, promote comfort, and prevent excessive respiratory effort in certain circumstances which may lead to patient self-induced lung injury, as was increasingly seen during the coronavirus infectious disease (COVID)-19 pandemic[18]. The utilization of ultra-protective ventilator settings during ECMO support poses challenges to traditional inhalational anesthetic delivery through orotracheal tubes due to excessively low minute ventilation[17].

During ECMO, circulating blood is oxygenated and decarboxylated by a membrane that is composed of hollow fibers. A sweep gas (typically blended oxygen) passes through these fibers to facilitate gas exchange (Figure 2). Case reports

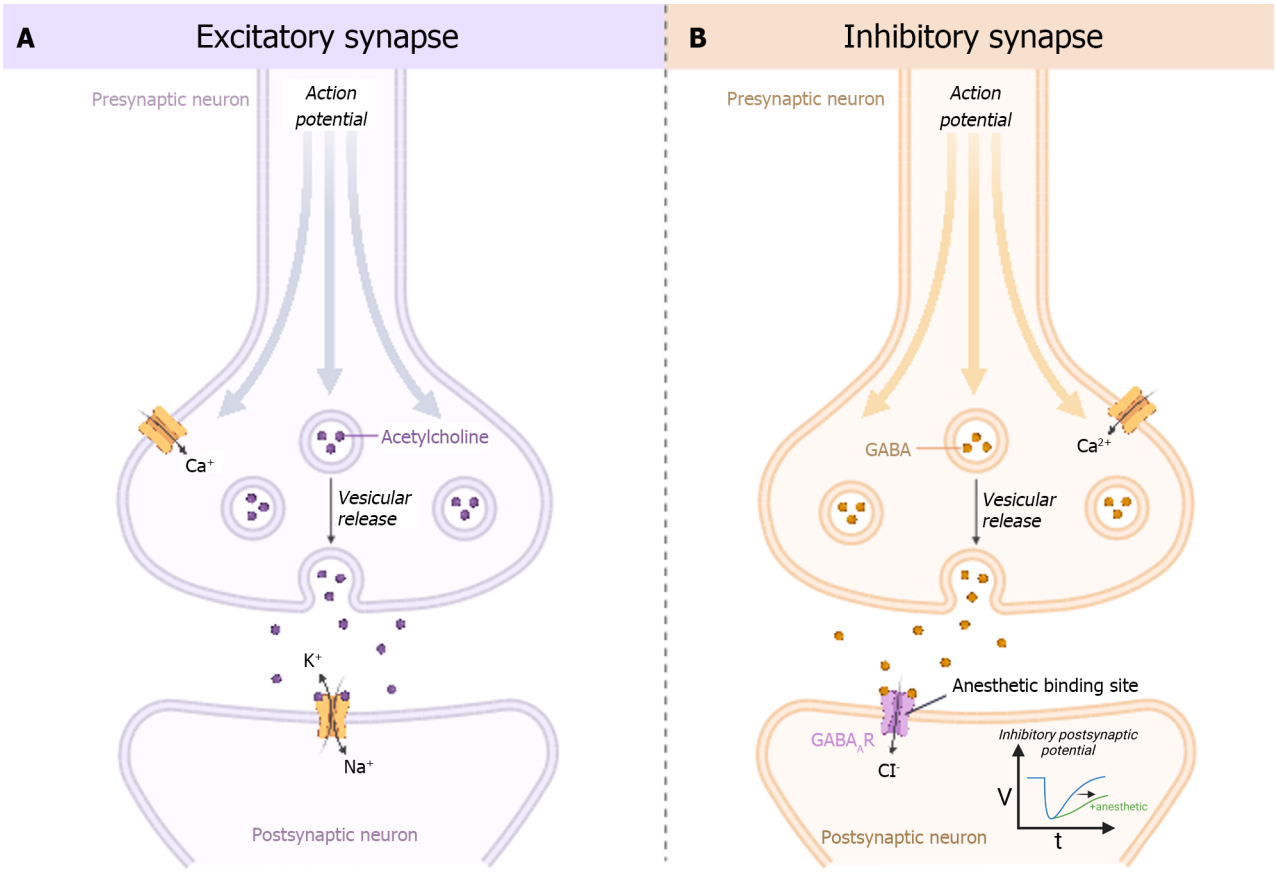

Figure 1 Volatile anesthetic mechanism of action. A: Excitatory neural synapse; B: Inhibitory neural synapse augmented by volatile anesthetic. Created with BioRender.com.

have described successful administration of sevoflurane (using the AnaConDa device)[19] and isoflurane (using an isoflurane vaporizer)[20] through direct insertion in the ECMO sweep gas airline, between the blender and the membrane oxygenator. The sweep gas flow rate can be used to calculate the anesthetic consumption and estimate the effective concentration[21]. While oxygenators constructed of polymethylpentene fibers are becoming increasingly popular in ECMO for their longer-term durability and reducing the 'plasma leakage' phenomenon, their non-porous (diffusion-based) surface appears to limit the transfer of volatile anesthetics[22,23]. Microporous polypropylene oxygenators may be preferred if delivering volatile anesthetics through the membrane during ECMO support. Modifying the ECMO circuity to deliver anesthetic gas requires careful considerations including a collection system for gas from the membrane gas outlet and any gas from the native expiration of the ventilator[19].

Malignant hyperthermia

Malignant hyperthermia (MH) is a rare but serious adverse effect of all inhaled anesthetics, except nitrous oxide, as well as depolarizing neuromuscular blockers, such as succinylcholine, whereby the skeletal muscles exhibit a hypermetabolic state[24]. It occurs seldom, less than once in the professional lifetime of an anesthesiologist (approximately 1 in every 250000 anesthetic exposures). Although rare, it can be a serious and deadly complication of volatile anesthetics, fortunately however, it is readily treatable when recognized. Despite evidence of a genetic link, it can also occur in individuals that don't have a genetic predisposition (no documented family history).

The features of MH are non-specific and include a rapidly increasing carbon dioxide level despite increased minute ventilation (usually the first sign), high fever (≥ 103°F), muscle rigidity, tachycardia, arrhythmias, hypotension, and a new unexplained lactic acidosis[24]. MH can be readily treated by stopping the offending agent, administering dantrolene, and providing supportive care[24]. Having an emergency treatment plan and pre-prepared kits available in the ICU is critical as it is an environment that may be less familiar with MH (Figure 3). There is an MH hotline to call in case of an emergency or questions, +1-800-644-9737.

APPLICATIONS IN THE ICU

Traditionally, intravenous-based anesthesia has been the mainstay for providing sedation in the ICU. With the development of specific devices to safely deliver volatile anesthetics, there has been growing interest in applying them in the ICU, without the need for traditional anesthesia machines that are used in operating theatres. In a general ICU

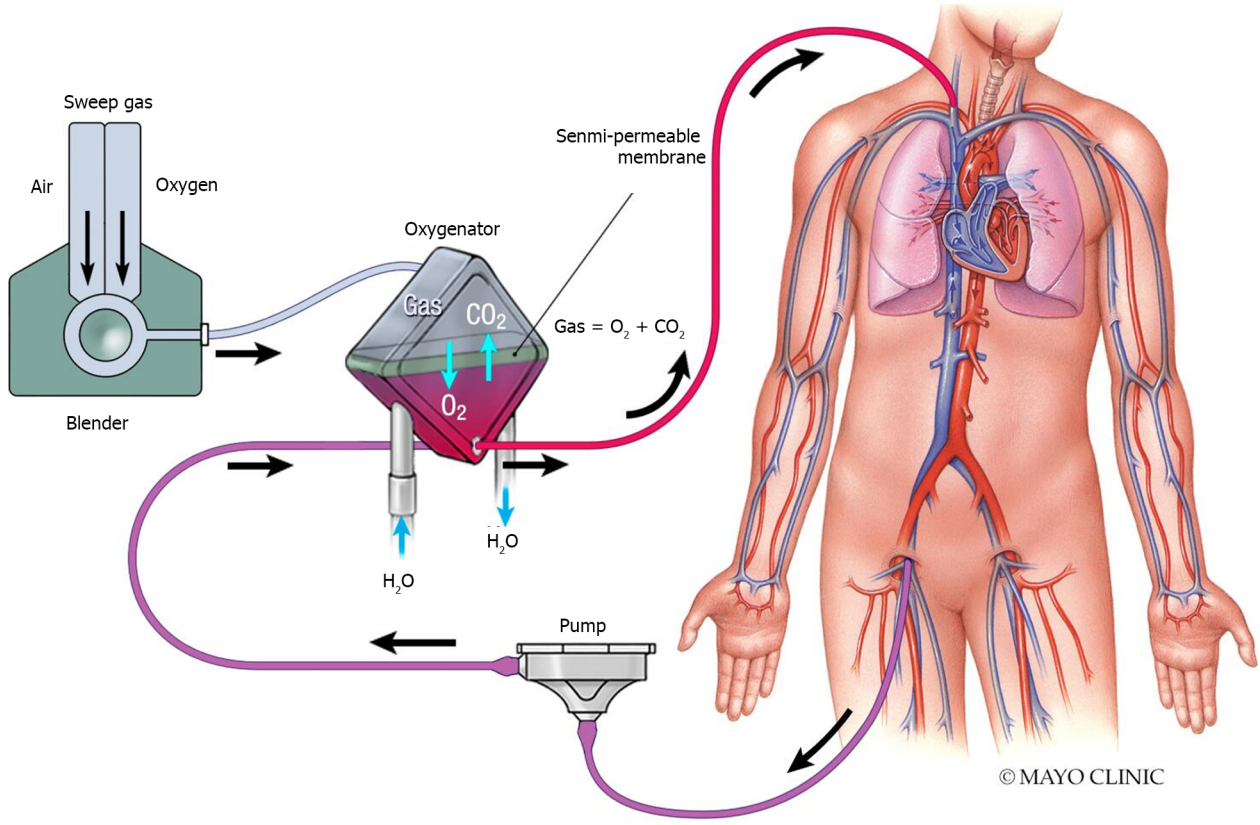

Figure 2 Depiction of how extracorporeal membrane oxygenation works in acute respiratory failure[17]. Citation: Wieruszewski PM, Ortoleva JP, Cormican DS, Seelhammer TG. Extracorporeal Membrane Oxygenation in Acute Respiratory Failure. Pulm Ther 2023; 9: 109-126 [PMID: 36670314 DOI: 10.1007/s41030-023-00214-2].

Figure 3 Example of a malignant hyperthermia kit for the intensive care unit.

population requiring mechanical ventilation, randomization to isoflurane using the AnaConDa device resulted in less opioid consumption, more frequent day 1 spontaneous breathing, and faster awakening with shorter time to extubation when compared to propofol[25]. A meta-analysis of 13 trials assessing volatile anesthesia in a variety of ICU clinical conditions found shorter awakening times and time to extubation, but no differences in length of stay[26]. The following sections will discuss specific conditions encountered in ICU practice that may be of particular interest for use of volatile anesthesia.

Short-term postoperative sedation

Although volatile anesthesia is commonly deployed throughout the operating theatres, continuation into the early postoperative setting following surgery has been a growing area of interest (Table 3). There have been a few trials of brief postoperative volatile anesthesia following non-cardiac operations[3,27,28], and several following cardiac operations that utilize cardiopulmonary bypass[29-34]. In general, use of volatile anesthetics upon arrival to the ICU for brief (few hours) sedation until appropriate for extubation, appears to allow for quicker awakening and faster time to extubation compared to propofol-based sedation (Table 3). Despite this, no study has demonstrated that this benefit results in any differences in ICU length of stay.

In patients undergoing cardiac surgery (mainly coronary artery bypass grafting) with use of cardiopulmonary bypass, some trials suggest a myocardial protective effect with postoperative volatile anesthesia[29,33], while others have shown no differences[32,34]. Furthermore, hemodynamics and use of vasoactive agents were also similar between volatile anesthetic and propofol groups.

Prolonged sedation during mechanical ventilation

The Society of Critical Care Medicine Pain Agitation and Delirium 2018 guidelines make no recommendations for the use of inhaled anesthetics for prolonged sedation due to lack of randomized control trial evidence[35]. There are several advantages to utilizing inhaled anesthetics for prolonged sedation during mechanical ventilation in the ICU, including associated opioid-sparing effects, increased time spent at goal sedation targets, decreased time to extubation, and ease of titration when compared to continuous intravenous sedation (Table 2)[36,37].

A 2016 retrospective cohort study by Bellgardt *et al*[38] compared surgical ICU patients receiving ventilation and sedation for at least 96 h *via* continuous infusion propofol and midazolam with or without inhaled isoflurane with an AnaConDa delivery device within 72 h of an initial intubation event. A Ramsay sedation score of 2-4 was targeted for all patients and the primary outcome of interest was inpatient mortality. One hundred twenty-eight patients were included in the intravenous sedation group, and 72 patients were in the intravenous plus inhaled anesthetic group over a 6-year time frame. Isoflurane utilization was associated with decreased in hospital mortality 40% *vs* 63%, adjusted odds ratio 0.39 (95%CI, 0.22-0.71, $P = 0.002$). While this study has many limitations, including its retrospective nature and mixed surgical population, it raises questions of the benefits of inhaled anesthetic use in the ICU for prolonged sedation[38].

A 2022 meta-analysis of 15 studies, including 1520 patients, compared inhaled *vs* intravenous anesthetics and their effect on patient outcomes. This study revealed similar mortality rates with inhaled anesthetics *vs* intravenous sedation but the used of inhaled anesthetics was associated with decreased duration of ventilation ($P = 0.03$), time to awakening ($P = 0.04$) and cardiac troponin levels ($P < 0.001$). These outcomes remained true in the subpopulations examined, including surgical *vs* medical ICU patients, as well as those treated with propofol *vs* other continuous intravenous sedatives[5].

Status asthmaticus

Status asthmaticus is defined as life-threatening bronchospasm refractory to treatment that has significant morbidity and mortality implications. Importantly, 21% of patients with status asthmaticus requiring mechanical ventilation die[39]. In a retrospective report of 30-year experience of management of status asthmaticus, 61.2% of patients required intubation and experienced an overall mortality of 0.4%[40]. Aside from the algorithmic managements of status asthmaticus that include hallmark use of short acting inhaled beta-agonists, systemic steroids, anticholinergics, and magnesium[41,42]. Advanced therapies such as venovenous ECMO and inhaled volatile anesthetics have been trialed and reported in case reports/series[43,44]. Volatile anesthetics are proposed to facilitate bronchorelaxation through direct relaxation of airway bronchial smooth muscles[45], beta-2-adrenergic stimulation, inhibition of inflammatory markers such as tumor necrosis factor alpha, transforming growth factor beta, and vascular endothelial growth factor[46], and inhibition of vagal-mediated reflexes. Volatile anesthetics may be delivered *via* direct inhalation, during mechanical ventilation, or through ECMO circuits as previously described[13,14,45-48]. Limitations to volatile anesthetic use in this context include limited availability of resources such as anesthesia machines outside the operating theatres, sufficient technology to integrate existing anesthetic conserving systems seamlessly and safely to ECMO circuitry, and trained personnel availability for the duration of treatment.

The majority of data for treatment of status asthmaticus with inhaled volatile anesthetics is in the pediatric population, although the concepts of mechanism and outcomes may be extrapolated to adults, evidence is lacking[41,49]. In a 2015 case series of three pediatric patients treated with volatile anesthetics showed use of isoflurane in addition to intubation and standard care for asthma resulted in safe use for 3-17 d, resulting in improved arterial carbon dioxide and tidal volumes. The only adverse effect reported was mild hypotension in one patient[41]. A recent retrospective, descriptive cohort of 45 pediatric ICU patients receiving isoflurane with or without ECMO showed improved arterial carbon dioxide levels and acidosis within four hours of anesthetic initiation[50].

Status epilepticus

Refractory status epilepticus is a severe subset of status epilepticus (continuous clinical/electroencephalogram-based

Table 3 Summary of short-term postoperative volatile anesthetic studies

Ref.	Treatment	Surgeries	Sedation duration	Time to awakening/extubation	Other outcomes
Non-cardiac surgery					
Bellgardt *et al*[3], 2019, Randomized trial	Isoflurane with MIRUS™ (*n* = 10)	Major surgery (aortic, pancreatic, esophagectomy, spinal fusion, hyperthermic intraperitoneal chemotherapy, necrotizing fasciitis)	17.9 (16.6–20.6) h	NR	Isoflurane had longest awakening times followed by sevoflurane, with desflurane the shortest (open eyes, follow verbal commands, extubation, tell birthday). Desflurane was most expensive followed by sevoflurane, with isoflurane the cheapest (per hour)
	Sevoflurane with MIRUS™ (*n* = 10)		16.5 (10.4–37.4) h	NR	
	Desflurane with MIRUS™ (*n* = 10)		18.8 (14.1–33.8) h	NR	
Jung *et al*[27], 2020, Prospective interventional	Sevoflurane with AnaConDa (*n* = 25)	Head and neck surgery with tracheostomy	771 ± 338.4 min	NR	Sevoflurane required less continuous opioid. Similar vasopressor use and length of stay
	Propofol (*n* = 24)		1508 ± 2074.7 min	NR	
Romagnoli *et al* [28], 2017, Prospective interventional	Sevoflurane with MIRUS™ (*n* = 62)	Laparoscopic and robotic-assisted noncardiac	3.33 (2.33–5.75) h	4 (2.2–5) min (awakening after drug cessation)	No adverse effects. Pollution < 1 ppm at all timepoints assessed
Cardiac surgery					
Hellström *et al* [29], 2011, Randomized trial	Sevoflurane with AnaConDa (*n* = 50)	Elective or subacute coronary artery bypass grafting using cardiopulmonary bypass	176 min	NR	Sevoflurane had less intense increase in troponin at 12 h. Similar hemodynamics and length of stay
	Propofol (*n* = 50)		221 min	NR	
Jerath *et al*[30], 2015, Randomized trial	Isoflurane or sevoflurane with AnaConDa (*n* = 67)	Elective coronary artery bypass grafting using cardiopulmonary bypass	NR	182 (140–255) min (extubation after ICU arrival)	No adverse effects. Similar hemodynamics and lengths of stay
	Propofol (*n* = 74)		NR	292 (210–420) min (extubation after ICU arrival)	
Röhm *et al*[31], 2008, Randomized trial	Sevoflurane with AnaConDa (*n* = 35)	Elective coronary artery bypass grafting using cardiopulmonary bypass	8.1 ± 3.5 h	9.0 ± 4.0 h (extubation after ICU arrival)	Sevoflurane had faster times of recovery after sedation cessation (eye opening, following commands, hand grip, and extubation). Similar ICU length of stay, sevoflurane with lower hospital length of stay
	Propofol (*n* = 35)		8.4 ± 4.2 h	12.5 ± 5.8 h (extubation after ICU arrival)	
Soro *et al*[32], 2012, Randomized trial	Sevoflurane with AnaConDa (*n* = 36)	Elective coronary artery bypass grafting using cardiopulmonary bypass	NR	NR	No differences in postoperative cardiac biomarkers, hemodynamics, or lengths of stay
	Propofol (*n* = 37)		NR	NR	
Steurer *et al*[33], 2012, Randomized trial	Sevoflurane with AnaConDa (*n* = 46)	Valve replacement with cardiopulmonary bypass	At least 4 h	NR	Sevoflurane had lower troponin T and creatine kinase concentrations on postoperative day 1
	Propofol (*n* = 56)		At least 4 h	NR	
Wąsowicz *et al* [34], 2018, Randomized trial	Isoflurane (*n* = 30) or sevoflurane (*n* = 30) with AnaConDa	Elective or urgent coronary artery bypass grafting using cardiopulmonary bypass	NR	172.1 ± 175.5 min (extubation after ICU arrival)	No difference in postoperative troponin values or ICU or hospital length of stay
	Propofol (*n* = 67)		NR	219.6 ± 104.9 min (extubation after ICU arrival)	

NR: Not reported; ICU: Intensive care unit.

seizure activity or recurrent seizures without recovery) that continues despite first and second line therapies[51]. Often prolonged sedation with barbiturates, propofol, and benzodiazepines is needed to break through this refractory condition. Volatile anesthetics pose as an option in the management of status epilepticus particularly in refractory states. Volatile agents apply their anticonvulsant properties through promotion of the inhibitory GABA-a pathways and inhibition of the excitatory NMDA pathways (Figure 1)[52,53]. In addition, with prolonged seizures NMDA receptors are upregulated resulting in a vicious cycle that potentiates glutamate-mediated excitotoxicity[54]. Volatile anesthetic gases counteract that through their cerebral protective properties with inhibition of this glutamate mediated NMDA excitotoxicity. In particular, isoflurane and desflurane have been shown to possess NMDA inhibitive properties.

A case report by Zhumadilov *et al*[55] reveals a remarkable response to isoflurane for the management of refractory status epilepticus. Reviews and case series showing efficacy of their use in pediatric and adult populations have also been reported[56-58]. With regards to which agents can be used, in general the majority of inhaled anesthetics result in electroencephalographic burst suppression with the best evidence surrounding isoflurane use. In particular, enflurane should be avoided as it lowers the seizure threshold and can induce seizure activity[59]. The epileptogenicity of sevoflurane has been scrutinized with conflicting evidence, where some studies reveal increased epileptiform discharges, and animal studies also reveal some epileptogenic effects[60-62].

Acute respiratory distress syndrome

ARDS is a pulmonary disorder defined by non-cardiogenic pulmonary edema, resulting in severe hypoxemia and is treated with protective mechanical ventilation and often requires deep levels of sedation to promote ventilation synchrony and prevent patient self-induced lung inury[63,64]. In 2020 with the COVID-19 pandemic, patients in ICUs across the world developed ARDS and had extremely high sedative requirements, and often required neuromuscular blocking agent administration to allow for lung protective ventilation[65,66].

Inhaled halogenated anesthetics have a potential multimodal benefit in ARDS, as they have opioid or other intravenous sedative agent sparing effects as well as potential for lung protective effects. Halogenated anesthetics in animal models have been shown to preserve epithelial tight junction integrity and decrease capillary leak, therefore decreasing direct acute injury to alveoli which is a hallmark effect of ARDS[67,68].

Several small case series have been published, showing promising effects of isoflurane and sevoflurane, with or without intravenous sedation, specifically in patients who were unable to reach optimal sedation goals on intravenous sedative agents alone[69-71]. This decrease in intravenous sedation use was critical at the peak of COVID-19 due to widespread drug shortages of commonly used sedative agents and continuous intravenous opioids. The use of inhaled anesthetics is attractive for their ability to spare the use of these agents in these challenging settings[72].

In the largest study to date of this population, Coupet and colleagues conducted a retrospective cohort study of 196 patients with COVID-19 ARDS from 10 European and United States centers; 85 patients received intravenous sedation only, 111 received intravenous and inhaled sedation[4]. Patients receiving inhaled sedation were administered it for a median of 5 d and it was most commonly sevoflurane. The primary outcome of interest was ventilation free days through 28 d. After propensity matching and multivariable adjustment, there were no differences in ventilation-free days between the two groups, although both groups had a median of 0 ventilation-free days at 28 d, highlighting the severity of illness in this cohort[4].

Conditions with very high sedative requirements

Similar to COVID-19 ARDS, several patient populations have extraordinarily high anesthetic requirements and would benefit from the opioid and sedative sparing effects of inhaled anesthetics, including those with burns, alcohol use, or high opioid use at baseline. Patients with significant alcohol, benzodiazepine or opioid tolerance at baseline have altered neurotransmitter sensitivity and typically require higher doses of sedatives to achieve sedation goals[73]. In small retrospective studies, isoflurane and sevoflurane have been shown to decrease opioid, propofol, and neuromuscular blockade requirements in patients with ARDS[69-71]. This makes inhaled anesthetics an attractive adjunctive agent in these patient populations.

Burn patients experience pharmacokinetic changes, systemic inflammation, and increased volume of distribution which alters drug metabolism and further complicates the ability to manage the severe pain they experience[74,75]. Sevoflurane has anti-inflammatory properties, wherein it down regulates interleukin-8; this is hypothesized to be beneficial in the highly inflammatory state post-burn. A study of 12 mechanically ventilated burn patients receiving sevoflurane for procedural sedation, such as dressing changes (2-4 h periods of sedation), compared to non-burn controls has been conducted to assess the pharmacokinetics in this population[76]. The authors concluded that use of sevoflurane in this population is safe but has altered metabolism and prolonged clearance. More studies are needed to assess the clinical utility of sevoflurane for pain management in this population[6].

GAPS AND ONGOING TRIALS

Although positive data are emerging leading to enthusiasm for use of volatile anesthesia in the ICU, barriers remain[77]. Staff education and development of safe devices and technology will be paramount to continued successful implementation of volatile anesthetics in the ICU. In addition, further development of technology, such that devices can be safely adapted to unique scenarios, such as integration with ECMO circuitry, is needed. And lastly, high quality studies assessing volatile anesthesia and intravenous anesthesia in the ICU, across various clinical conditions are needed.

Currently, there are two parallel phase 3, multicenter, randomized, controlled, open-label, assessor blinded trials ongoing in the United States to evaluate the efficacy and safety of inhaled isoflurane delivered *via* the Sedaconda anesthetic conserving device-S compared to intravenous propofol for sedation of mechanically ventilated intensive care unit adult patients (NCT05312385, NCT05327296). Additional ongoing trials include a multicenter, randomized, controlled, open-label trial in France evaluating the frequency of occurrence of delirium of intravenous propofol compared to inhaled sedation with isoflurane (NCT04341350) and another multicenter, randomized, controlled, open-label trial in Canada evaluating the effects on ventilatory parameters and survival between intravenous sedation and inhaled sedation with either isoflurane or sevoflurane (NCT04415060).

CONCLUSION

In conclusion, evidence is accumulating suggesting benefits of employing volatile anesthetics for patients in the ICU with indications ranging from ARDS to status epilepticus. While volatile anesthetics are widely utilized in operating theatres worldwide, their underutilization in the ICU persists, potentially influenced by a multitude of structural or medical considerations and lingering uncertainties on quality of evidence supporting benefits. Of note, technological developments are changing the landscape, whereby the simplification of volatile anesthetic handling poses a possible avenue for broader implementation in ICU settings, particularly for conditions refractory to traditional intravenous modalities.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Erin D Wieruszewski 0000-0002-7703-2233; Mariam ElSaban 0000-0003-4194-051X; Patrick M Wieruszewski 0000-0002-5871-5186; Nathan J Smischney 0000-0003-1051-098X.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Shock index and its variants as predictors of mortality in severe traumatic brain injury

Randhall B Carteri, Mateus Padilha, Silvaine Sasso de Quadros, Eder Kroeff Cardoso, Mateus Grellert

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Randhall B Carteri, Department of Nutrition, Centro Universitário CESUCA, Porto Alegre 94935-630, Brazil

Mateus Padilha, Department of Analysis and Systems Development, Centro Universitário CESUCA, Porto Alegre 94935-630, Brazil

Silvaine Sasso de Quadros, Department of Nutrition, Hospital Pronto Socorro de Porto Alegre, Porto Alegre 90040-192, Rio Grande do Sul, Brazil

Eder Kroeff Cardoso, Department of Physiotherapy, Hospital Pronto Socorro de Porto Alegre, Porto Alegre 90040-192, Rio Grande do Sul, Brazil

Mateus Grellert, Institute of Informatics, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre 91501-970, Rio Grande do Sul, Brazil

Corresponding author: Randhall B Carteri, PhD, Postdoc, Professor, Researcher, Department of Nutrition, Centro Universitário CESUCA, Silvério Manoel da Silva, 160-Colinas, Cachoeirinha-RS, Porto Alegre 94935-630, Brazil. rcarteri@outlook.com

Abstract

BACKGROUND

The increase in severe traumatic brain injury (sTBI) incidence is a worldwide phenomenon, resulting in a heavy disease burden in the public health systems, specifically in emerging countries. The shock index (SI) is a physiological parameter that indicates cardiovascular status and has been used as a tool to assess the presence and severity of shock, which is increased in sTBI. Considering the high mortality of sTBI, scrutinizing the predictive potential of SI and its variants is vital.

AIM

To describe the predictive potential of SI and its variants in sTBI.

METHODS

This study included 71 patients (61 men and 10 women) divided into two groups: Survival (S; n = 49) and Non-survival (NS; n = 22). The responses of blood pressure and heart rate (HR) were collected at admission and 48 h after admission. The SI, reverse SI (rSI), rSI multiplied by the Glasgow Coma Score (rSIG), and Age multiplied SI (AgeSI) were calculated. Group comparisons

included Shapiro-Wilk tests, and independent samples *t*-tests. For predictive analysis, logistic regression, receiver operator curves (ROC) curves, and area under the curve (AUC) measurements were performed.

RESULTS

No significant differences between groups were identified for SI, rSI, or rSIG. The AgeSI was significantly higher in NS patients at 48 h following admission (S: 26.32 ± 14.2, and NS: 37.27 ± 17.8; $P = 0.016$). Both the logistic regression and the AUC following ROC curve analysis showed that only AgeSI at 48 h was capable of predicting sTBI outcomes.

CONCLUSION

Although an altered balance between HR and blood pressure can provide insights into the adequacy of oxygen delivery to tissues and the overall cardiac function, only the AgeSI was a viable outcome-predictive tool in sTBI, warranting future research in different cohorts.

Key Words: Head trauma; Critical patient; Neuro-cardio axis; Predictive tool; Clinical practice

Core Tip: Patients who suffer severe head trauma are also affected by altered balance between heart rate and blood pressure which influences oxygen delivery to tissues and the overall cardiac function. Although previous studies indicated that shock index (SI) and its variants could predict the outcomes following traumatic brain injury (TBI) the studies were conducted in patients with different severities of injury. Therefore, when evaluating patients who suffered a severe TBI (sTBI), the SI and its variants are not a viable outcome-predictive tool in sTBI, due to similar responses in both surviving and non-surviving patients. However, the Age multiplied SI was a viable outcome-predictive tool in sTBI, warranting future research in different cohorts.

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INTRODUCTION

Presently recognized as a significant public health issue, traumatic brain injury (TBI) commonly results in persistent neurological dysfunction[1,2]. TBI is defined as an alteration in normal brain function resulting from biomechanical forces, caused by rapid acceleration or deceleration of the brain due to motorcycle or automobile accidents; impact resulting from the brain's collision due to falls, motorcycle and automobile accidents, or contact sports; changes in pressure and air displacement due to explosions; and also, by the penetration of projectiles or objects into the brain[2,3]. The initial pathophysiological changes resulting from primary mechanical damage can trigger deleterious secondary effects, including progressive neurodegeneration[3]. Additionally, cardiovascular complications are common after TBI, including disturbances in systemic blood pressure, cardiac arrhythmias, and left ventricular dysfunction[4]. Therefore, as these abnormalities are associated with increased morbidity and mortality in TBI, it is plausible that persistent cardiocirculatory dysfunction may underlie some of the pathological features of chronic TBI.

TBI is classified as mild, moderate, or severe, and it can lead to premature death, cognitive alterations, and neuropsychiatric impairments, often compromising the quality of life of surviving individuals[1,5]. This classification is a combination of various criteria, with the Glasgow Coma Scale (GCS) being the most commonly used tool[6]. The severity level holds prognostic value but does not necessarily predict the patient's final level of functioning. The pathophysiological mechanisms associated with TBI involve primary injury resulting from mechanical or inertial damage to both white and gray matter, causing membrane rupture, content release, and diffuse axonal injury[7,8]. Secondary damage refers to the progression of changes associated with the primary brain injury, such as the persistent activation of a series of neurotoxic events, leading to structural damage progression[7]. Thus, the extent and severity of secondary damage are proportional to the trauma intensity and the location of the primary insult, in addition to mechanisms influencing secondary damage, including cardiovascular impairment[9]. Importantly, a complex set of neural pathways, termed the "neuro-cardiac axis," explains cardiac rhythm and hemodynamic disturbances following head trauma[10]. This interaction between the brain and the heart is evident during both primary (due to sympathetic hypertonus, arrhythmias, and cerebral perfusion pressure) and secondary injury (due to catecholamine release, microvascular and myocardial disturbances), as evidenced by conditions such as subarachnoid hemorrhage[4]. In this context, the shock index (SI) is a physiological parameter that quantifies the relationship between heart rate (HR) and systolic blood pressure[11]. This index serves as an indicator of cardiovascular status and is widely used as a tool to assess the presence and severity of shock or circulatory disturbances in various medical conditions, including TBI[12,13].

Hence, to the best of our knowledge, there are no studies that assess the role of SI and its variants as a predictor tool of mortality in severe TBI (sTBI) patients without multiple central injuries. The findings of this study can guide future clinical procedures to ensure a positive impact on the prognosis and quality of life of this population. Therefore, this study aims to describe the predictive potential of SI and its variants as an outcome-predictive tool in sTBI patients.

MATERIALS AND METHODS

Study design

This was a prospective observational study by convenience sampling conducted between January 2019 and December of 2022 at the Pronto-Socorro Hospital, a trauma reference center at Porto Alegre, RS, Brazil.

This study followed the ethical precepts, guidelines, and norms established in Resolution No. 466 of 2012 of the National Health Council, and was carried out only after approval by the Health Research and Ethics Committee of the Municipal Health Secretariat Office of Porto Alegre (CEP SMSPA; registration number: 3.912.623). Patients were identified through registration numbers, which only serves to validate the individuality of the information. The sample was determined in a non-probabilistic way for convenience, selected through the inclusion and exclusion criteria described below, without any discrimination in the selection of individuals or exposure to unnecessary risks. Patients admitted to the adult trauma intensive care units (ICUs) aged 18 years or older who required enteral or parenteral nutritional therapy were included. The following were excluded from the study: Patients with a GCS score of 9 to 15; patients who were diagnosed with cervical, thoracic or abdominal trauma; patients who received only oral diet, and those with incomplete medical records or records due to lack of data. Of 342 patients admitted to the trauma ICU during the explored period, 71 patients were included in this study.

The study was carried out in the adult trauma ICU of the Hospital de Pronto Socorro de Porto Alegre, with retrospective data, covering the period from January 2019 to December 2022. Data collection was carried out using the institutional Hospital Information System, which includes the complete electronic medical record of the patient. The collected variables were: GCS score, injury description, age, sex, days of fasting, body mass, estimated height, blood pressure, and HR parameters. Body mass index (BMI = Body mass/Height^2) was calculated to classify the patients according to the criteria of the World Health Organization[14]. The SI, rSI, and rSIG were calculated as the ratio of HR to systolic blood pressure (SBP) (SI = HR/SBP), the ratio of SBP to HR (rSI = SBP/HR), the score of rSI × GCS, and age multiplied SI (AgeSI = Age × SI) respectively.

Statistical analysis

The general description of the selected data is available through simple and relative frequencies. The normality of distributions of all variables were evaluated using the Shapiro-Wilk test. Student's t test for independent or the Pearson's Chi-Square test was used to compare data between groups. Spearman's rho was used to evaluate the correlation between different variables. To evaluate the predictive potential of SI, rSI, rSIG, and AgeSI we used logistic regression, where regression coefficients (B) were obtained for each variable. When the Wald test values were significant, the odds ratio was calculated to indicate the percentage changes (Exp(B) – 100). Also, receiver operator curves (ROC) analysis was performed. Significant correlations and differences were considered where $P < 0.05$. All data were analyzed using the Statistical Package for Social Sciences 26.0 statistical program.

RESULTS

Table 1 provides the characteristics of the 72 patients included in this study, which were allocated in two distinct groups: Survival (S; $n = 49$) and non-survival (NS; $n = 22$). Analysis of the variables indicated that the groups were significantly different regarding mean age (S: 40.51 ± 17.4, and NS: 50.73 ± 14.6; $P = 0.013$), number of days in hospital (S: 28.76 ± 14.6, and NS: 14.36 ± 16.8; $P = 0.001$). No differences were observed for the other variables, except for the presence of COPD in the NS group ($P = 0.032$).

Table 2 presents the data regarding blood pressure, HR, and different SI. The HR and the SI at 48 h after admission significantly differed between S and NS patients ($P = 0.036$, and $P = 0.03$, respectively). No differences were observed for the other variables, including the different SI, except for the AgeSI. The AgeSI was significantly higher in NS patients at 48 h following admission (S: 26.32 ± 14.2, and NS: 37.27 ± 17.8; $P = 0.016$). The logistic regression and area under the receiver operating characteristic curve (AUROC) results are shown in Table 3. When evaluating the significance and the odds ratio to explore further the relationship of different SI with survival odds, no relationship was identified. In patients with sTBI (Figure 1), the AUROC analysis indicated that the predictive accuracy of SI and its variants were insignificant, except for AgeSI at 48 h, where the AUROC curve for predicting mortality was 0.727.

DISCUSSION

The present study evaluated the role of SI as a variable to predict the outcomes of sTBI patients coinfected patients. Notably, the different SI were not predictors of outcomes for severe head injury patients, despite the significantly different HR and SI responses at 48 h following admission between S and NS patients. However, the AgeSI could be a

Table 1 Characteristics of patients with severe head injury

	Survival (*n* = 49)		Non-survival (*n* = 22)		*P* value[1]
Age (years), mean ± SD	40.51	17.4	50.73	14.6	0.013
Days in MV, mean ± SD	28.76	14.6	14.36	16.8	0.001
Fasted days, mean ± SD	13.78	8.7	7.68	6.4	0.002
Days in hospital, mean ± SD	28.76	14.6	14.36	16.8	0.001
					P value[2]
Sex, *n* (%)					0.161
Male, *n* (%)	44	89.8%	17	77.3%	
Female, *n* (%)	5	10.2%	5	22.7%	
Injury type, *n* (%)					0.607
Closed	35	71.4%	17	77.3%	
Open	14	28.6%	5	22.7%	
Injury cause, *n* (%)					0.408
Fall	13	26.5%	10	45.5%	
Transit accident	18	36.7%	4	18.2%	
Assault	13	26.5%	6	27.3%	
Gunshot	4	8.2%	1	4.5%	
Other	1	2.0%	1	4.5%	
Associated injuries, *n* (%)					0.658
None	36	73.5%	19	86.4%	
Thoracic	4	8.2%	1	4.5%	
Arms	1	2.0%	0	0.0%	
Legs	5	10.2%	2	9.1%	
Spine	3	6.1%	0	0.0%	
Craniotomy procedure, *n* (%)					0.822
No	34	77.3%	15	68.2%	
Yes	14	31.8%	7	31.8%	
Body mass index (kg/cm²), *n* (%)					0.761
Underweight	4	8.2%	2	13.6%	
Eutrophic	25	51.0%	0	54.5%	
Overweight	14	28.6%	2	18.2%	
Grade I Obese	6	12.2%	2	13.6%	
Comorbidities, *n* (%)					
COPD	0	0	2	9.1%	0.032
Asma	1	0.02	0	0.0%	0.513
T2DM	1	0.02	2	9.1%	0.172
SAH	4	8.2%	2	9.1%	0.897
EVA	1	0.02	1	4.5%	0.555
AD	2	4.1%	1	4.5%	0.928

[1]Student's t test.
[2]Pearson's Chi-Square test.
MV: Mechanical ventilation; COPD: Chronic obstructive pulmonary disease; DM: Type 2 diabetes mellitus; SAH: Systemic arterial hypertension; EVA:

Encephalic vascular accident; AD: Alzheimer's disease.

Table 2 Blood pressure, heart rate and different shock indexes (mean ± SD)

	Survival (*n* = 49)		Non-survival (*n* = 22)		*P* value
SBP-24 h (mmHg)	135.59	36.5	138.95	40.1	0.739
DBP-24 h (mmHg)	81.27	23.5	85.38	25.2	0.526
HR-24 h (bpm)	88.22	25.4	88.68	29.0	0.949
SBP-48 h (mmHg)	131.47	27.6	127.20	25.0	0.536
DBP-48 h (mmHg)	67.77	12.1	72.33	15.0	0.257
HR-48 h (bpm)	82.61	18.5	93.95	19.9	0.036
SI-adm	0.70	0.3	0.69	0.3	0.901
SI-48 h	0.65	0.2	0.79	0.3	0.03
rSI-adm	1.70	0.8	1.78	1.0	0.742
rSI-48 h	1.66	0.5	1.44	0.5	0.106
rSIG-adm	10.45	5.9	11.02	7.7	0.758
rSIG-48 h	10.26	4.8	9.29	4.8	0.452
AgeSIG-adm	28.02	16.8	34.40	17.1	0.152
AgeSIG-48 h	26.32	14.2	37.27	17.8	0.016

SBP: Systolic blood pressure; HR: Heart rate; DBP: Diastolic blood pressure; SI: Shock index; rSI: Reverse shock index; rSIG: rSI multiplied by the Glasgow Coma Score; AgeSIG: Age multiplied SI.

Table 3 Logistic regression and receiver operator curves analysis parameters

	Sig.	Exp(B)	95%CI for EXP(B)		Odds ratio (%)	AUC	*P* value
			Inferior	Superior			
SI-adm	0.895	0.885	0.144	5.444	-11.5	0.487	0.864
SI-48 h	0.129	7.592	0.554	104.036	659.2	0.606	0.176
rSI-adm	0.727	1.107	0.626	1.956	10.7	0.517	0.832
rSI-48 h	0.194	0.436	0.125	1.527	-56.4	0.395	0.180
rSIG-adm	0.652	1.018	0.942	1.101	1.8	0.537	0.637
rSIG-48 h	0.641	0.973	0.867	1.092	-2.7	0.473	0.727
AgeSIG-adm	0.153	1.022	0.992	1.052	2.2	0.639	0.071
AgeSIG-48 h	0.015	1.044	1.008	1.082	4.4	0.727	0.003

SI: Shock index; rSI: Reverse SI; rSIG: rSI multiplied by the Glasgow Coma Score; AgeSIG: Age multiplied SI; AUC: Area under the curve.

useful tool to predict mortality, showing statistical difference among surviving and non-surviving sTBI patients, and significant predictive value.

The rationale behind the SI is rooted in the understanding that an altered balance between HR and blood pressure can provide insights into the adequacy of oxygen delivery to tissues and the overall cardiac function[15]. Therefore, these physiological responses are directly implicated in survival of TBI patients, due to the relationship with the extent of both primary and secondary damage mechanisms, including restriction of flow in the long pituitary portal vessels after injury [16]. The predictive value of the SI in determining mortality in critically ill patients (including TBI patients) has been a subject of investigation in recent studies. Notably, studies such as those conducted by Cannon *et al*[17] and McNab *et al* [18] have contributed to our understanding of the prognostic significance of the SI in this population. Cannon *et al*[17] conducted a retrospective analysis of TBI patients, elucidating the association between an elevated SI and increased mortality. Their findings underscored the utility of the SI as an early prognostic marker, with increased values indicative

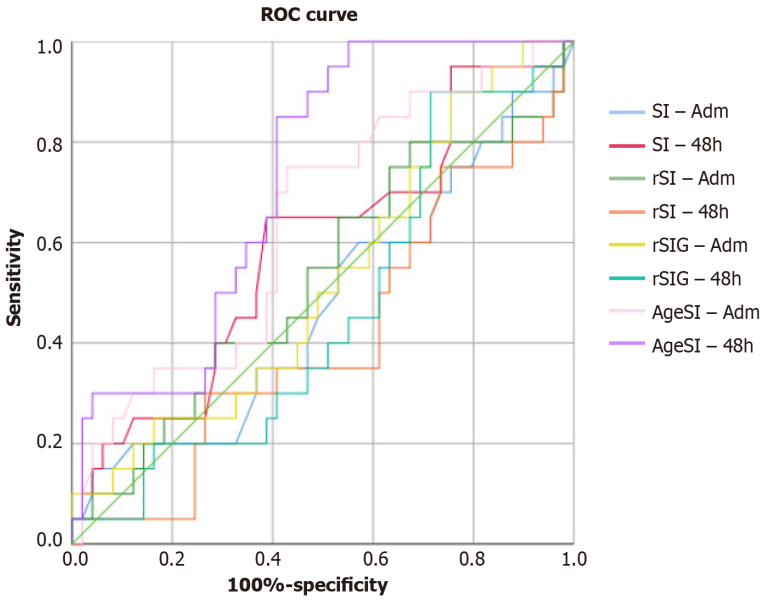

Figure 1 Area under the receiver operator curve analysis. ROC: Receiver operator curve; SI: Shock index; rSI: Reverse shock index; rSIG: rSI multiplied by the Glasgow Coma Score; AgeSIG: Age multiplied SI.

of higher mortality risk. The study highlighted the clinical relevance of SI assessment in identifying TBI patients at heightened risk of adverse outcomes[17].

Building upon this foundational work, McNab *et al*[18] conducted a prospective study to further investigate the predictive capabilities of the SI in severe TBI patients. Their results affirmed a significant association between an elevated SI on admission and increased mortality, emphasizing the potential utility of this simple yet informative metric in risk stratification and early intervention[18]. In an earlier investigation, Rady *et al*[19] explored the predictive value of the SI in a broader trauma population, including TBI cases. Their prospective study demonstrated the sensitivity of the SI in identifying patients at risk of adverse outcomes. Although not specific to TBI, the results provided insights into the potential applicability of the SI as a valuable tool for early prognostication[19].

Recently, Wu *et al*[12] contributed to the literature by conducting a retrospective analysis focusing on the SI and reverse SI (rSI) multiplied by GCS as a predictor of mortality in 2438 patients with isolated head injury. Like the present study, the patients who died were significantly older that those who survived. However, the analysis included patients with different levels of TBI, as indicated by significant differences in the GCS. The study affirmed the independent association between an elevated SI and mortality, indicating that the rSI is superior to SI as a predictor of mortality in TBI, with comparable predictive power to both the Trauma and Injury Severity Score and Revised Trauma Score, further supporting its potential role in risk stratification for TBI patients. Comparatively, in the present study we investigated sTBI patients, which are more prone to have a higher SI score due to the nature of the injury mechanisms. Thus, no differences were identified for SI and its variants among S and NS patients. Interpreting traditional vital signs and the SI proves challenging when applied to the elderly population. Advanced age is associated with lower HR responses and elevated systolic blood pressures, leading to an escalation in false-negative values and influencing SI outcomes with increasing age. To address this issue, previous research suggested that SI multiplied by age (AgeSI) is a better predictor of mortality following traumatic injury of an elderly patient, we also included this variant in the analysis[20,21]. In the present study, AgeSI showed tendency to significance at admission, and was significantly different at 48 h following admission, showing significant predictive value. Our findings those of Kim *et al*[22], showing that the predictive power of the AgeSI for in-hospital mortality was higher in geriatric trauma patients. Therefore, AgeSI is a viable predictive tool in sTBI which is supported by previous research validating AgeSI index[23,24].

This study is subject to several limitations. Firstly, it relied on a retrospective analysis. Secondly, the exact time profile from injury occurrence to mortality was not measured. While the SI proves effective in predicting short-term mortality, the lack of a precise timeline from injury to mortality, due to database constraints, limits the comprehensive predictive capacity of the SI assessment. Rather than presenting an exact time profile, our evaluation focused on the SI's predictive efficacy for mortality during the emergency department stay and the overall in-hospital period, respectively. Thirdly, the database did not furnish information regarding the use of anti-hypertensive medications (such as beta blockers), introducing a potential factor that may impact the validity of SI assessment. Also, the data regarding previous comorbidities rely on the information given by the patients or their caregivers and may present inconsistencies. As for strengths, we highlight the investigation in sTBI patients, the study's originality, and the importance of this study evaluating the SI and its variants, an important tool for prognosis in the clinical treatment of critical patients.

CONCLUSION

In conclusion, only AgeSI was a viable predictor of mortality following severe head injury. Therefore, future studies should continue to search for cost-effective clinical tools that can predict survival and other outcomes in sTBI patients, considering the cohort-specific characteristics.

ARTICLE HIGHLIGHTS

Research background

Patients who suffer severe head trauma are also affected by altered balance between heart rate (HR) and blood pressure which influences oxygen delivery to tissues and the overall cardiac function. Although previous studies indicated that shock index (SI) and its variants could predict the outcomes following traumatic brain injury (TBI) the studies were conducted in patients with different severities of injury.

Research motivation

To the best of our knowledge, there are no studies that assess the role of SI and its variants as a predictor tool of mortality in severe TBI (sTBI) patients without multiple central injuries. The findings of this study can guide future clinical procedures to ensure a positive impact on the prognosis and quality of life of this population.

Research objectives

This study aims to describe the predictive potential of SI and its variants as an outcome-predictive tool in sTBI patients.

Research methods

This was a prospective observational study conducted at the Pronto-Socorro Hospital, a trauma reference center at Porto Alegre, RS, Brazil, including 71 patients were included in this study. The study included retrospective data, covering the period from January 2019 to December 2022. The collected variables were: Glasgow Coma Scale (GCS) score, injury description, age, sex, days of fasting, body mass, estimated height, blood pressure, and HR parameters. Body mass index (BMI = body mass/Height^2) was calculated to classify the patients according to the criteria of the World Health Organization. The SI, reverse SI (rSI), and rSI multiplied by the Glasgow Coma Score (rSIG) were calculated as the ratio of HR to systolic blood pressure (SBP) (SI = HR/SBP), ratio of SBP to HR (rSI = SBP/HR), the score of rSI × GCS, and age multiplied SI (AgeSI = Age × SI) respectively. Group comparisons included Shapiro-Wilk tests and independent samples *t*-tests. For predictive analysis, logistic regression, receiver operator curves (ROC) curves, and area under the curve (AUC) measurements were performed.

Research results

No significant differences between groups were identified for SI, rSI, or rSIG. The AgeSI was significantly higher in non-survival (NS) patients at 48 h following admission (Survival: 26.32 ± 14.2, and NS: 37.27 ± 17.8; $P = 0.016$). Both the logistic regression and the AUC following ROC curve analysis showed that only AgeSI at 48 h was capable of predicting sTBI outcomes. For AgeSI at 48 h, the AUROC curve for predicting mortality was 0.727.

Research conclusions

Patients who suffer severe head trauma are also affected by altered balance between HR and blood pressure which influences oxygen delivery to tissues and the overall cardiac function. Although previous studies indicated that SI and its variants could predict the outcomes following TBI the studies were conducted in patients with different severities of injury. Therefore, when evaluating patients who suffered a sTBI, the SI and its variants are not a viable outcome-predictive tool in sTBI, due to similar responses in both surviving and non-surviving patients. However, the AgeSI was a viable outcome-predictive tool in sTBI, warranting future research in different cohorts.

Research perspectives

Future studies should evaluate the AgeSI as an outcome-predictive tool in sTBI.

FOOTNOTES

Author contributions: Carteri RB was responsible for concept and design, data collection, statistical analysis, and manuscript writing; Padilha M was responsible for data collection, statistical analysis, and manuscript writing; de Quadros SS and Kroeff E were responsible for data collection, manuscript writing, and key revisions; Grellert M was responsible for the concept and design, statistical analysis, manuscript writing and critical editing.

Institutional review board statement: This project was approved by the Research Ethics Committee of Hospital Pronto Socorro de Porto Alegre (number CEP SMSPA; registration number: 3.912.623).

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ORCID number: Randhall B Carteri 0000-0003-4124-9470; Mateus Grellert 0000-0003-0600-7054.

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ORIGINAL ARTICLE

Retrospective Study

Predictive value of thrombocytopenia for bloodstream infection in patients with sepsis and septic shock

Xia Li, Sheng Wang, Jun Ma, Su-Ge Bai, Su-Zhen Fu

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Xia Li, Jun Ma, Su-Ge Bai, Su-Zhen Fu, Department of Critical Care Medicine, Xingtai People Hospital, Xingtai 054001, Hebei Province, China

Sheng Wang, Department of Physiology, Hebei Collaborative Innovation Center for Cardio-cerebrovascular Disease, Hebei Medical University, Shijiazhuang 050000, Hebei Province, China

Corresponding author: Xia Li, MS, Doctor, Department of Critical Care Medicine, Xingtai People Hospital, No. 16 Hongxing Street, Xingtai 054001, Hebei Province, China.
lix0518@163.com

Abstract

BACKGROUND

Thrombocytopenia is common in patients with sepsis and septic shock.

AIM

To analyse the decrease in the number of platelets for predicting bloodstream infection in patients with sepsis and septic shock in the intensive care unit.

METHODS

A retrospective analysis of patients admitted with sepsis and septic shock in Xingtai People Hospital was revisited. Patient population characteristics and laboratory data were collected for analysis.

RESULTS

The study group consisted of 85 (39%) inpatients with bloodstream infection, and the control group consisted of 133 (61%) with negative results or contamination. The percentage decline in platelet counts (PPCs) in patients positive for pathogens [57.1 (41.3-74.6)] was distinctly higher than that in the control group [18.2 (5.1–43.1)] ($P < 0.001$), whereas the PPCs were not significantly different among those with gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection. Using receiver operating characteristic curves, the area under the curve of the platelet drop rate was 0.839 (95%CI: 0.783-0.895).

CONCLUSION

The percentage decline in platelet counts is sensitive in predicting bloodstream infection in patients with sepsis and septic shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection.

Key Words: Platelet counts; Thrombocytopenia; Bloodstream infection; Sepsis; Shock

Core Tip: Thrombocytopenia is common in sepsis and septic shock, but there are few reports on the diagnostic value of thrombocytopenia in bloodstream infection. Our results found that the rate of platelet drop but not the lowest platelet count has a high predictive ability for bloodstream infection in patients with sepsis or septic shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection. Dynamic detection of platelet counts appears to be an early alert for the clinician in identifying the site of infection and evaluating serious infection. This will guide the performance of blood cultures and the use of empirical antibiotics.

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INTRODUCTION

Bloodstream infection (BSI) is a life-threatening condition caused by the presence of microorganisms, generally bacteria or fungi, in blood. The ability to diagnose BSI early can have a significant impact on patient outcomes. Platelets constantly roam the vascular system and play an active role in pathogen capture. Platelets can kill bacterial pathogens directly *via* microbicidal proteins, known as thrombocidins[1]. Platelets are able to release cytokines, recruit leukocytes, interact with bacteria and the endothelium, and promote microthrombi formation[2,3]. Either a relative or an absolute decrease in the platelet number is often seen in patients who most likely develop sepsis and septic shock. However, few reports have documented the relationship between a drop in platelet counts and BSI. The aims of this study were to determine the diagnostic ability of the percentage decline of platelet counts (PPCs) for predicting the presence of BSI and evaluating the cut-off point for detecting BSI.

MATERIALS AND METHODS

We conducted a retrospective cohort study at Xingtai People's Hospital, Hebei Province, China, which has 2200 beds serving local residents. Adult patients (age ≥ 18 years) who were admitted to the intensive care unit (ICU) with a diagnosis of sepsis or septic shock and stayed at least 3 d in the ICU were included in the study. The exclusion criteria included haematologic disease, acute bleeding, history of platelet disorders, cirrhosis, and use of chemotherapy (in the last 30 d prior to admission). The following variables were collected from the electronic medical records: patient population characteristics (age, sex); underlying disease (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease); laboratory data (aetiology, daily platelet counts, white blood cell count, neutrophil count, haemoglobin, C-reactive protein, procalcitonin, blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, serum bilirubin, serum albumin, fibrinogen, D-dimer, prothrombin time, activated partial thromboplastin time); source of infection; primary diagnosis, mechanical ventilation, requirement for renal replacement therapy; and Acute Physiology and Chronic Health Evaluation II score (APACHE-II score). This study was a retrospective clinical data analysis and patients did not undergo invasive procedures.

According to the sepsis 3 guidelines[4], sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The clinical criteria for sepsis include suspected or documented infection and an acute increase in two or more Sequential Organ Failure Assessment points as a proxy for organ dysfunction. Septic shock was defined by the clinical criteria of sepsis and vasopressor therapy needed to elevate mean arterial pressure ≥ 65 mmHg and lactate > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation. Blood cultures were drawn from the patients within 1 h after ascertaining the patient had sepsis or septic shock. BSI was defined as one or more bacterial species in blood samples. Bloodstream infection caused by coagulase-negative staphylococci was determined after careful evaluation by the doctor according to the clinical manifestations and treatment effect. Negative specimen culture was defined as negative culture for 5 d. Daily platelet counts were recorded from the day the blood cultures were taken. If the platelet counts were performed twice or more within 24 h, we recorded the lowest count for analysis. The rate of the drop in platelets was calculated by the formula $(Platelet_1 - Platelet_{low})/Platelet_1$, where $Platelet_1$ is the Platelet value at the time of drawing blood cultures, and $Platelet_{low}$ is the lowest platelet value within the following 3 d.

RESULTS

Patient characteristics

During the study period, a total of 218 patients with sepsis and septic shock were enrolled. Of these, 85 had positive blood cultures, and 133 had negative cultures or contamination. Demographic, clinical and laboratory characteristics are presented in Tables 1 and 2. The median age was 63 years, and 122 (56%) patients were male. There was no difference in age, sex, underlying comorbidities (hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease), APACHE II score, mechanical ventilation, renal replacement therapy, or 28-d mortality between patients with positive blood cultures and those with negative blood cultures or contamination. However, patients with cerebrovascular disease had fewer positive blood cultures (P = 0.044). Regarding the primary source of infection, respiratory tract infections were the most common infections in patients in the ICU, which were detected in 101 patients (46.3%). Patients with positive blood cultures were more often admitted with hepatobiliary and urinary infections and less often with respiratory tract infections (Table 1).

Laboratory findings

At admission, patients with positive blood cultures had higher levels of procalcitonin, neutrophils, and C-reactive protein but not white blood cell counts than those with negative cultures or contamination (Table 2). Marked differences were also found in the prothrombin time, activated partial thromboplastin time, D-dimer, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and creatinine levels. These indicators were significantly higher in patients with positive blood cultures than in those with negative cultures or contamination. No significant differences were found for fibrinogen, urea nitrogen, serum albumin, haemoglobin, or glycosylated haemoglobin (P > 0.05).

Among the 85 bacteraemia episodes, 24 were caused by gram-positive bacteria, 59 by gram-negative bacteria and 2 by fungi. The most commonly isolated bacterial species were *Escherichia coli* (n = 36) and *Klebsiella pneumoniae* (n = 15), which accounted for 60% of blood infections (Table 3).

Daily platelet count

The daily platelet count over time was recorded as the median (25^{th}, 75^{th} percentile) (Figure 1). The median platelet count dropped to a nadir of 60 (range, 30-128) × 109/L in the group positive for pathogens and 148 (range, 73-200) × 109/L in the group negative for pathogens or contamination on the fourth day after admission to the ICU and subsequently increased. The platelet count did not differ between the two groups on the first day. From Day 2 to Day 7, the platelet count in the pathogen-positive group was significantly lower than that in the control group (P < 0.05).

The PPC% in different groups

In the present study, the percentage decline in PPC in patients who were positive for pathogens [57.1 (41.3-74.6)] was distinctly higher than that in patients who were negative or had contamination [18.2 (5.1–43.1)] (P < 0.001). There were also significant differences in the lowest platelet count between the patients who were positive for pathogens [54 (27-119)] and those who were negative or contaminated [140 (77-182)] (P < 0.001). However, in the subgroup of positive with pathogens, the PPCs were not significantly different among the gram-positive bacteraemia, gram-negative bacteraemia, and fungi groups (P > 0.05) (Figure 2).

Receiver operating characteristic curves of serum biomarkers

Receiver operating characteristic (ROC) curves were created for PPCs to predict BSI (Figure 3). The areas under the ROC curves (AUCs) were calculated to evaluate the biomarkers (PPC, procalcitonin, lowest platelet count, C-reactive protein, and neutrophil percentage) to determine the presence of bacteraemia. PPC had high diagnostic utility for predicting BSI. Its predictive ability was greater than that of procalcitonin; the AUC of PPC was 0.839 (95%CI: 0.783-0.895). Additionally, that of procalcitonin was 0.718 (95%CI: 0.644-0.791), whereas C-reactive protein and neutrophil percentage did not detect BSI (P > 0.05). Using the lowest platelet count, the area under the ROC curve was 0.274 (95%CI: 0.201-0.347), showing a low, not significant accuracy for BSI diagnosis. At a cut-off point of 35%, the sensitivity and specificity of PPC were 0.84 and 0.73, respectively, and the Youden index was 0.57. At cut-off points of 50% and 60%, the sensitivity was reduced to 0.63 and 0.44, respectively, but yielded high specificities of 0.82 and 0.90.

DISCUSSION

Early recognition of BSI and establishing early treatment are important for patients with infection. In this retrospective cohort, we demonstrated that the ratio of platelet drop was independently associated with BSI. This is the first study to investigate the association between these parameters. The study included 218 sepsis and sepsis shock patients, and their demographic variables and clinical and laboratory characteristics are described. Patients with BSI were associated with the severity of sepsis and sepsis shock, as indicated by higher inflammatory biomarkers (procalcitonin, C-reactive protein, neutrophils), higher percentage decline of platelet counts, liver and kidney function injury, and coagulation disorder (prothrombin time, activated partial thromboplastin time, D-dimer), compared to patients who did not have a BSI. It has been reported that bacteraemia is an independent risk factor for nosocomial infection-related mortality[5]; however, in our study, 28-d mortality was not significantly different between bacteraemia and non-bacteraemia patients. This could be due to respiratory failure caused by a respiratory infection, which was detected in 46.3% of patients in the ICU in our

Table 1 Patient characteristics *n* (%)

Characteristic	All patients (*n* =218)	Blood culture results		*P* value
		Negative or contamination (*n* = 133)	Positive with pathogen (*n* = 85)	
Age (yr)	63 (53–73)	64 (53–73)	62 (52–70)	0.253
Sex (male/female)	218 (122/96)	133 (81/52)	85 (41/44)	0.066
Comorbidities				
Hypertension	79 (36.2)	50 (37.6)	29 (34.1)	0.603
Diabetes	49 (22.5)	29 (21.8)	20 (23.5)	0.766
Cardiovascular disease	23 (10.6)	17 (12.8)	6 (7.1)	0.18
COPD	16 (7.3)	13 (9.8)	3 (3.5)	0.085
Cerebrovascular disease	34 (15.6)	26 (19.5)	8 (9.4)	0.044
Primary diagnosis for cultures				
Respiratory	101 (46.3)	81 (60.9)	20 (23.5)	< 0.001
Intestinal	50 (22.9)	28 (21.1)	22 (25.9)	0.408
Urogenital	33 (15.1)	12 (9.0)	21 (24.7)	0.002
Hepatobiliary	21 (9.6)	6 (4.5)	15 (17.6)	0.001
Skin/soft tissue	5 (2.3)	3 (2.3)	2 (2.4)	1.0
Other	8 (3.7)	3 (2.3)	5 (5.9)	0.308
APACHE II	20 (14-25)	19 (14-25)	20 (14-27)	0.533
Mechanical ventilation (yes/no)	218 (156/62)	133 (100/33)	85 (56/29)	0.137
Renal replacement (yes/no)	218 (29/189)	133 (13/120)	85 (16/69)	0.055
28-d mortality	81 (37.2)	46 (34.6)	35 (41.2)	0.326

COPD: Chronic obstructive pulmonary disease; APACHE: Acute physiology and chronic health.

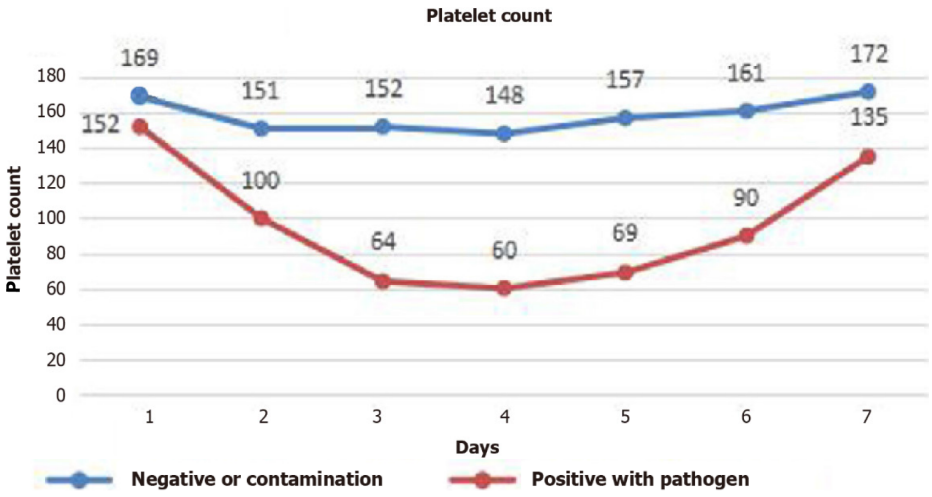

Figure 1 Platelet count over time stratified according to blood culture results. Data are median (25th, 75th percentile).

study, it was the main cause of death and these patients had a low incidence of BSI. We recorded the daily platelet count and found that the median duration of thrombocytopenia occurred on Day 4 after admission to the ICU (Figure 1), which is in accordance with the results of previous research[6,7].

In our study, the most common organism isolated was *Escherichia coli*, with *Klebsiella pneumoniae* being the second most common pathogen in blood infections. This is consistent with a previous finding showing that *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae* and *Streptococcus pneumoniae* were the most commonly isolated organisms in community-acquired BSIs[8]. In recent years, it has been reported that respiratory tract, urinary tract, and intra-

Table 2 Patient laboratory characteristics

Characteristic	All patients (*n* = 218)	Blood culture results		*P* value
		Negative or contamination (*n* = 133)	Positive with pathogen (*n* = 85)	
PCT (ng/mL)	6.9 (1.1-32.1)	2.85 (0.4-16.6)	16.8 (4.1-112.3)	< 0.001
CRP (mg/mL)	113.3 (47.9-174.3)	99.4 (41.1-168.3)	128.1 (68.5-189.7)	0.047
WBC (× 10^9/L)	12.3 (8.1–17.8)	11.7 (8.8–16.8)	13.1 (7.5–21.7)	0.404
Neutrophils (%)	90.1 (82.5-93.5)	88.9 (83.4-92.3)	92.2 (82.3-94.7)	0.029
Haemoglobin (g/L)	109.6 ± 23.8	109.9 ± 24	109.2 ± 23.6	0.824
HBA1C	5.9 (5.4-7.2)	6.0 (5.6-7.1)	5.8 (5.3-8.6)	0.7
PT (s)	14.4 (12.7-16.7)	13.9 (12.7-15.7)	15.5 (12.7-17.5)	0.012
APTT (s)	34.5 (30.2-41.5)	33.3 (29.6-38.0)	37.2 (30.2-44.8)	0.005
Fib (g/L)	3.94 (3.0-4.97)	3.95 (3.19-5.26)	3.93 (2.85-4.87)	0.344
D-dimer (μg/mL)	6.37 (2.62-12.34)	5.33 (2.19-10.94)	8.06 (3.93-13.81)	0.02
Alanine aminotransferase (U/L)	31.8 (18–61.2)	24.2 (14.8–47.5)	43.4 (23.1–113.9)	< 0.001
Aspartate aminotransferase (U/L)	46.2 (29.6–87.1)	37.9 (25.8–70)	67.2 (35.2–170.4)	< 0.001
Total bilirubin (μmol/L)	15.6 (9.1–29.1)	13.5 (8.9–23.7)	20.6 (10.7–49)	0.009
Serum albumin (g/L)	28.8 (24.4-31.7)	28 (24.2-32.2)	29.4 (25-31.5)	0.444
BUN (mmol/L)	9.9 (6.0–15.3)	9.2 (5.9–14.2)	10.8 (6.2–15.9)	0.147
Cr (μmol/L)	99.6 (67.3–180)	89.1 (62.4–146)	134.5 (84.7–221)	0.001

PCT: Procalcitonin; CRP: C-reactive protein; WBC: White blood cell; HBAIC: Glycosylated haemoglobin; PT: Prothrombin time; APTT: Activated partial thromboplastin time; Fib: Fibrinogen; BUN: Blood urea nitrogen; Cr: Creatinine.

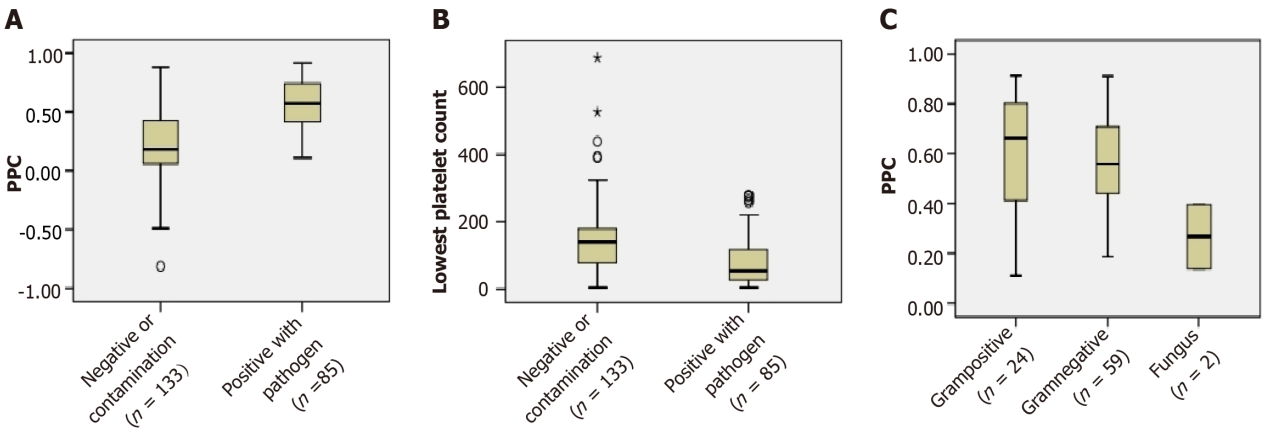

Figure 2 Box plot showing the percentage decline of platelet counts and lowest platelet count. A: Eighty-five bacterial infection episodes showed a higher percentage decline of platelet count (PPC); B: Lower levels of platelet count than nonbacterial events ($P < 0.001$) by Mann-Whitney *U* test; C: The PPC was not significantly different in the group with gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection ($P > 0.05$). Data are presented with median lines, 25- and 75-percentile boxes, and 10- and 90-percentile error bars. PPC: The percentage decline of platelet counts. The (*) and (o) in the figure are Scatter data.

abdominal infections are the main sources of sepsis and sepsis shock[9,10], and gram-negative bacteraemia has a higher frequency in the ICU[11]. Similarly, our study also showed that respiratory tract infection was the main reason for admission to the ICU but the patients had a lower rate of BSIs. However, the urogenital and hepatobiliary tract have a higher incidence of BSIs in ICU patients.

Our results confirm that the rate of platelet drop but not the lowest platelet count has a high predictive ability for BSI. It has been reported that procalcitonin levels are a good biomarker for bacterial infections, and procalcitonin has been introduced into clinical use[12,13]. Similarly, our study supports this option. Comparing other inflammatory markers, the diagnostic utility of PPC (AUC of 0.839) was significantly higher than that of procalcitonin (AUC of 0.718), C-reactive

Table 3 Microorganisms isolated from blood cultures

Microorganism	No. (%) isolated from blood cultures
Gram-positive bacteria	24 (28.2)
Staphylococcus aureus	6 (7.1)
Staphylococcus epidermidis	3 (3.5)
Staphylococcus haemolyticus	2 (2.4)
Staphylococcus hominis	2 (2.4)
Staphylococcus caprae	1 (1.2)
Enterococcus faecium	5 (5.9)
Streptococcus pyogenes	3 (3.5)
Streptococcus viridans	1 (1.2)
Enterococcus gallinarum	1 (1.2)
Gram-negative bacteria	59 (69.4)
Escherichia coli	36 (42.3)
Klebsiella pneumoniae	15 (17.6)
Pseudomonas aeruginosa	3 (3.5)
Aeromonas sobria	2 (2.4)
Enterobacter cloacae	1 (1.2)
Klebsiella oxytoca	1 (1.2)
Acinetobacter lwoffii	1 (1.2)
Fungus	2 (2.4)
Candida albicans	2 (2.4)

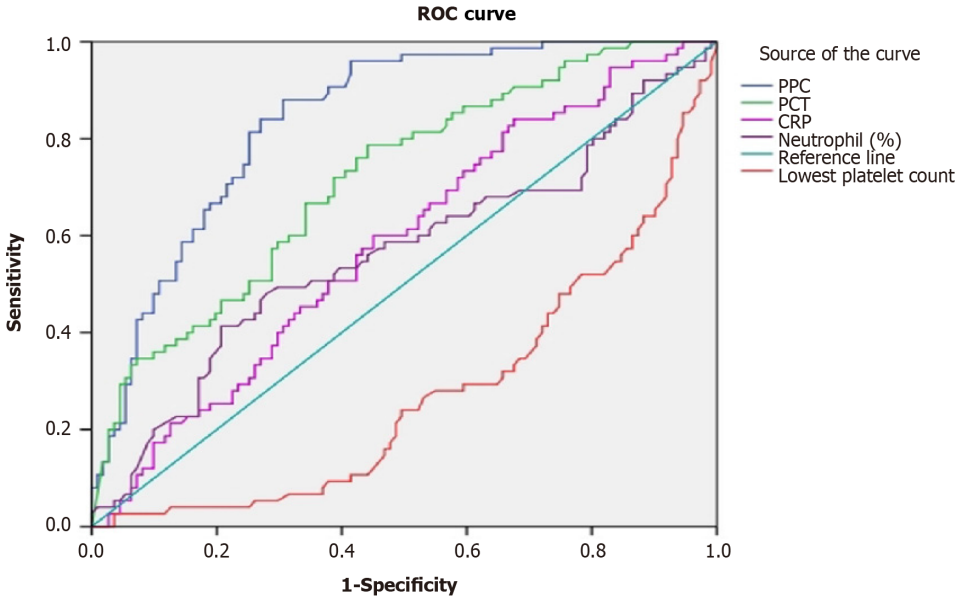

Figure 3 Receiver operating characteristic curves of serum biomarkers for the positive diagnosis of bacterial species in critically ill patients with clinical sepsis and sepsis shock. ROC: Receiver operating characteristic; PCT: Procalcitonin; CRP: C-reactive protein.

protein (AUC of 0.583) and neutrophils (AUC of 0.564). A cut-off point of 35% for PPC achieved a sensitivity of 84% and a specificity of 73%, whereas a cut-off point of 50% was correlated with a sensitivity of 62.7% and a specificity of 82%. A cut-off point of 60% reduced the sensitivity to 44%, but the specificity reached 90.1%. Therefore, clinicians should consider BSIs in sepsis and sepsis shock patients with a rapid drop in platelet count.

Thrombocytopenia is very common in patients with sepsis and sepsis shock, and there are several putative mechanisms, as stated below. First, the interactions between bacteria and platelets cause the consumption of platelets. Bacteria can bind to platelets *via* receptors either directly or indirectly, suggesting that they may induce aggregation, which has been described for *Streptococcus sanguinis, S. epidermidis*, or *S. pneumoniae* infections[14]. Preclinical findings from murine models suggested that platelets bind to adherent neutrophils through Toll-like receptor 4 and form neutrophil extracellular traps (NETs). NETs have the greatest capacity for bacterial trapping and ensnare bacteria within the vasculature[15]. In addition to containing pathogens, human and murine platelets can exert direct microbicidal activity, such as releasing platelet microbicidal proteins to kill pathogens[16,17]. Second, bacterial infections cause damage to the vascular endothelial lining and the release of inflammatory factors, accelerating adhesion, removal and immune-mediated destruction of platelets. Third, bacterial infections cause marrow depression, decreasing the production of platelets.

Our study has the following limitations: (1) We only recorded platelet changes within 7 d after admission to the ICU in sepsis and sepsis shock patients and did not consider changes in platelets in patients with secondary infection during ICU hospitalization, which may affect mortality; (2) In our study, the median time of the platelet count dropping to a nadir was on Day 4. However, the platelet counts were very low in some patients when they came to the hospital, and their platelets dropped to the lowest value on Day 2 after admission, which affected the ratio of platelet decline; and (3) We used culture-based methods as the gold standard for the diagnosis of BSI, and the initiation of empirical antimicrobial therapy in some patients significantly reduced the sensitivity of blood cultures. Future studies should determine if there is a drop in platelet count in experimental animals with BSI.

CONCLUSION

In conclusion, the percentage decline in platelet counts is sensitive in predicting BSI in patients with sepsis and sepsis shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection. Dynamic detection of platelet counts appears to be an early alert for the clinician in identifying the site of infection and evaluating serious infection. This will guide the performance of blood cultures and the use of empirical antibiotics.

ARTICLE HIGHLIGHTS

Research background

Either a relative or an absolute decrease in the platelet number is often seen in patients who most likely develop sepsis and septic shock. However, few reports have documented the relationship between a drop in platelet counts and bloodstream infection (BSI).

Research motivation

To determine whether decreased platelet counts are an early alert in identifying the site of infection and evaluating serious infection.

Research objectives

The aims of this study were to determine the diagnostic ability of the percentage decline of platelet counts (PPC) for predicting the presence of BSI and evaluating the cut-off point for detecting BSI.

Research methods

A retrospective analysis of patients admitted with sepsis and septic shock in Xingtai People Hospital was revisited. Patient population characteristics and laboratory data were collected for analysis.

Research results

The percentage decline in platelet counts in patients positive for pathogens [57.1 (41.3-74.6)] was distinctly higher than that in the control group [18.2 (5.1–43.1)] ($P < 0.001$), whereas the PPC was not significantly different among patients with gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection. Using receiver operating characteristic curves, the area under the curve of the platelet drop rate was 0.839 (95%CI: 0.783-0.895).

Research conclusions

The percentage decline in platelet counts is sensitive in predicting blood stream infection in patients with sepsis and septic shock. However, it cannot identify gram-positive bacteraemia, gram-negative bacteraemia, and fungal infection.

Research perspectives

Future studies should determine whether there is a drop in platelet count in experimental animals with BSI and clarify the underlying mechanism.

FOOTNOTES

Co-corresponding authors: Xia Li and Su-Zhen Fu.

Author contributions: Li X, Wang S, and Fu SZ conceived, designed and refined the study protocol; Ma J and Bai SG were involved in the data collection; Li X and Fu SZ analyzed the data; Li X wrote the paper; Wang S polished the language; Li X and Fu SZ contributed equally to this work as co-corresponding authors. Li X proposed, designed and conducted platelets analysis, performed data analysis and wrote the paper. Fu SZ was responsible for patient screening, enrollment, data analysis and paying for language polishing fees, both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-corresponding authors.

Institutional review board statement: According to the ethics committee review process, the paper entitled "The predictive value of thrombocytopenia for bloodstream infection in patients with sepsis and septic shock" was submitted for review, We agree that it conform to the principles of the CFDA, GCP, ICH-GCP, declaration of Helsinki and the requirement of the medical ethics and the relevant laws and regulations, not to the safety of the subjects, the research scope of influence or scientific quality, suitable for quick review process. The audit conclusion agreed to conduct clinical research.

Informed consent statement: This article was a retrospective clinical data analysis with no human interventions, our ethical committee agreed to the study and we did not require signed informed consent form(s) or document(s).

Conflict-of-interest statement: We also confirm that all the listed authors have seen and approved the submitted manuscript. The authors do not have any possible conflicts of interest.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at lix0518@163.com.

Country/Territory of origin: China

ORCID number: Xia Li 0000-0002-7274-1241.

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ORIGINAL ARTICLE

Prospective Study

Adding vortexing to the Maki technique provides no benefit for the diagnosis of catheter colonization or catheter-related bacteremia

Leonardo Lorente, Maria Lecuona Fernandez, Adriana González-Mesa, Judith Oliveras-Roura, Cristina Rosado, Pablo Cabrera, Emma Casal, Alejandro Jiménez, María Luisa Mora, Ana Madueño

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Leonardo Lorente, Adriana González-Mesa, Judith Oliveras-Roura, Cristina Rosado, Pablo Cabrera, María Luisa Mora, Intensive Care Unit, Hospital Universitario de Canarias, La Laguna 38320, Spain

Maria Lecuona Fernandez, Emma Casal, Ana Madueño, Microbiology and Infection Control Service, Hospital Universitario de Canarias, La Laguna 38320, Spain

Alejandro Jiménez, Research Unit, Hospital Universitario de Canarias, La Laguna 38320, Spain

Corresponding author: Leonardo Lorente, MD, PhD, Medical Assistant, Intensive Care Unit, Hospital Universitario de Canarias, Ofra s/n, La Laguna 38320, Spain. lorentemartin@msn.com

Abstract

BACKGROUND

A previous study compared vortexing and Maki techniques for the diagnosis of catheter-related bloodstream infection (CRBSI), and concluded that vortexing was not superior to Maki method.

AIM

To determine whether the combined use of vortexing and Maki techniques provides profitability versus the Maki technique for the diagnosis of catheter tip colonization (CTC) and CRBSI.

METHODS

Observational and prospective study carried out in an Intensive Care Unit. Patients with suspected catheter-related infection (CRI) and with one central venous catheter for at least 7 days were included. The area under the curve (AUC) of the Maki technique, the vortexing technique and the combination of both techniques for the diagnosis of CTC and CRBSI were compared.

RESULTS

We included 136 episodes of suspected CRI. We found 21 cases of CTC of which 10 were also CRBSI cases. Of the 21 CTC episodes, 18 (85.7%) were diagnosed by Maki technique and vortexing technique, 3 (14.3%) only by the technique of Maki, and none only by technique of vortexing. Of the 10 CRBSI episodes, 9 (90.0%) were diagnosed by the techniques of Maki and vortexing, 1 (10.0%) was diagnosed only by the technique of Maki, and none only by the technique of

vortexing. We no found differences in the comparison of AUC between the technique of Maki and the combination of Maki and vortexing techniques for the diagnosis of CTC (P = 0.99) and CRBSI (P = 0.99).

CONCLUSION

The novel finding of our study was that the combined use of vortexing and Maki techniques did not provide profitability to the technique of Maki alone to CRBSI diagnosis of.

Key Words: Vortexing; Maki; Bloodstream infection; Colonization

Core Tip: A previous study compared vortexing and Maki techniques for the diagnosis of catheter-related bloodstream infection (CRBSI), and concluded that vortexing was not superior to Maki the method. The novel finding of our study was that the combined use of vortexing and Maki techniques did not provide profitability to the technique of Maki alone to the diagnosis of CRBSI.

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INTRODUCTION

Different motives are responsible for the need of a central venous catheter (CVC), such as the monitorization of hemodynamic status or the administration of medications, fluids, parenteral nutrition or blood products. However, different risks are attributed to the use of CVC, for example, catheter-related bloodstream infection (CRBSI) that involves increasedmortality, assistant costs and morbidity[1-3].

The semiquantitative Maki technique, due to its simplicity, is considered the standard technique for the diagnosis of catheter tip colonization (CTC)[4]. However, as it consists of rolling the catheter tip across the agar (detecting the microorganism from the outer surface of the catheter tip), it has the potential disadvantage that it could not detect the microorganism from the inner surface. Thus, false negative of CTC could appear in the Maki technique of patients with endoluminal colonization. Quantitative techniques (such as vortexing or sonication) for CTC diagnosis could have a potential advantage over the Maki technique due to their potential ability to detect CTC by endoluminal mechanism (which is important in long term catheters) and not only by exoluminal mechanism[5-8]. However, all quantitative methods are more time consuming than the Maki technique, so its use in clinical microbiology laboratories is not widespread.

To our knowledge, there is only one study reporting data about the comparison between the vortexing quantitative technique and the Maki's semiquantitative technique for the diagnosis of CRBSI, and it concluded that vortexing was not superior to the Maki method[9].

The same strength of recommendations and quality of evidence (A-II) have been stablished for the Maki technique and the vortexing technique for the diagnosis of intravascular catheter-related infection (CRI) in recent guidelines[10,11].

A previous study were compared vortexing and Maki techniques in the diagnosis of CRBSI[9]; however, this study did not compare the combined use of vortexing and Maki over only the Maki technique for the diagnosis of CTC and CRBSI, and this was the novel objective of our study.

MATERIALS AND METHODS

Design and subjects

This prospective and observational study was carried with the approval of the Institutional Ethic Committee of the Hospital Universitario de Canarias (Tenerife, Spain). Patient recruitment was performed in the Intensive Care Unit of this hospital between April 2022 and September 2022 with informed consent signed by the patients or a member of their family.

Patients with suspicion of CRI and with long term CVC (at least 7 d) were included. CRI was suspected when a patient developed a new episode of fever (temperature ≥ 38ºC) or sepsis (according to Sepsis-3 Consensus criteria of 2016[12]). We used CVC type ARROWg^{+}ard Blue® (Arrow, Reading, PA, United States), which were impregnated on chlorhexidine-silver sulfadiazine on the external and internal surfaces).

Variables recorded

For each suspected CRI, the age and sex of the patient and the place and time of CVC were recorded. In addition, intensive care unit (ICU) admission diagnosis, personal history of diabetes mellitus, chronic obstructive pulmonary disease, asthma, smoking, chronic liver disease, hematological tumor, human immunodeficiency virus or solid tumor were recorded. In addition, we recorded the use of renal replacement, corticosteroids or immunosuppressants previously to ICU admission, and the use of corticosteroids, parenteral nutrition or propofol at the time of suspected CRI. Finally, we also registered death within 30 days of suspected CRI.

Sample collections

We collected paired catheter tip samples, blood samples and necessary clinical samples from each patient. Paired peripheral vein blood samples were collected 15 min apart with 10 mL of blood in each sample. Catheter tip samples were taken; and for this, the skin surrounding the insertion site was previously rubbed with 2% chlorhexidine and the tip was cut with sterile scissors (5 cm of distal segment). Initially, the distal segment of the catheter tip was cultured using the Maki technique and subsequently using the vortex technique. For the semiquantitative Maki technique, the distal segment of the catheter tip was plated on a blood agar plate[4]. For the quantitative vortexing technique, the distal segment of the catheter tip was placed with 1 mL of brain-heart infusion broth in a vortexing device and vortexed for 1 min. After vortexing for 1 min, 0.1 mL of that suspension was seeded on blood agar[9]. We excluded patients without culture with Maki tip technique, culture with vortex tip technique, and blood cultures.

Definitions

We use the criteria of European Centre for Disease Prevention and Control for definitions of infections[13]. We considered CTC when a significant growth on the CVC tip of a microorganism was obtained by semi-quantitativemethod of Maki (≥ 15 colony-forming units)[4] or by quantitative method of vortexing (≥ 1000 colony-forming units)[9]. CRBSI was defined as the presence of the same recognized pathogen in the blood culture and in the CVC tip without no other apparent source of infection. Two positive blood cultures (obtanied in a separation of 48 h) for a common skin contaminant (*Micrococcus spp., Coagulase-negative staphylococci, Propionibacterium acnes, Corynebacterium spp.* and *Bacillus spp.)* were required.

Statistical analysis

We reported categorical variables as frequencies (%) and continuous variables as medians (25%-75%). Categorical variables were compared using the chi-square test and continuous variables by the Mann-Whitney *T* test. The area under the curve (AUC) of the Maki technique, the vortexing technique and the combination of both techniques for the diagnosis of CTC and CRBSI were compared using the method of DeLong *et al*[14]. We carried out **s**tatistical analyses with SPSS 17.0 software (SPSS Inc., Chicago, IL, United States) and we considered *P* values lower than 0.05 as significant.

RESULTS

We included 136 episodes of suspected CRI. We found 21 cases of CTC of which 10 were also cases of CRBSI. We found that CVC that developed CRBSI (n = 10) showed higher CVC time (P = 0.02) compared to those that did not develop it (n = 126); however, no other significant differences between CVC who did or did not develop CRBSI were found (Table 1).

We found 21 episodes of CTC and 10 episodes of CRBSI. Of the 21 episodes of CTC, 18 (85.7%) were diagnosed by the techniques of Maki and vortexig, 3 (14.3%) were diagnosed only by the technique of Maki, and none wasdiagnosed only by the technique of vortexig (Table 2). Of the 10 episodes of CRBSI, 9 (90.0%) were diagnosed by the techniques of Maki and vortexing, 1 (10.0%) was diagnosed only by the technique of Maki technique, and none was detected only by the technique of vortexing (Table 3).

The AUC for CTC diagnosis was 100% (95%CI = 97%-100%; P < 0.001) to the technique of Maki, 93% (95%CI = 87%-97%; P < 0.001) to the technique of vortexing and 100% (95%CI = 97%-100%; P < 0.001) by the combination of techniques. No differences had in the comparison of AUC between the technique of Makiand the combination of techniques (P = 0.99) for CTC diagnosis.

The AUC for CRBSI diagnosis was 96% (95%CI = 91%-98%; P < 0.001) to with the technique of Maki, of 91% (95%CI = 85%-96%; P < 0.001) with the techniqe of vortexing and 96% (95%CI = 91%-98%; P < 0.001) with the combination of techniques. No differences had in the comparison of AUC between the technique of Maki and the combination of techniques (P = 0.99) for CRBSI diagnosis.

The microorganisms responsible for CTC were the following: *Staphylococcus epidermidis* 6 (2 with CRBSI), *Staphylococcus haemolyticus* 3 (1 with CRBSI), Methicillin-sensitive *Staphylococcus aureus* 1 (1 with CRBSI), Methicillin-resistant *Staphylococcus aureus* 1 (1 with CRBSI), *Pseudomonas aeruginosa* 2 (2 with CRBSI), *Klebsiella spp.* 3 (2 with CRBSI), *Acinetobacter spp.* 1, *Serratia* 1, *Candida albicans* 2, *Candida glabrata* 1 (1 with CRBSI).

DISCUSSION

To our knowledge, there is only one study reporting data on the comparison between the quantitative vortexing technique and the semiquantitative Maki technique for the diagnosis of CRBSI, and it concluded that vortexing was not

Table 1 Characteristics of central venous catheter with suspicion of catheter-related infection that developed or not catheter-related bloodstream infection

Data	Non CRBSI (*n* = 126)	CRBSI (*n* = 10)	*P* value (CRBSI *vs* non)
Time of CVC (d) [median (p 25-75)]	9 (7-12)	12 (10-18)	0.02
Site of CVC, *n* (%)			0.19
Subclavian	28 (22.2)	3 (30.0)	
Jugular	62 (49.2)	2 (50.0)	
Femoral	36 (28.6)	5 (50.0)	
Age (yr, p 25-75)	65 (57-70)	65 (58-75)	0.50
Sex female, *n* (%)	30 (23.8)	1 (10.0)	0.45
Admission diagnostic, *n* (%)			0.74
Medical	73 (57.9)	7 (70.0)	
Surgical	39 (31.0)	2 (20.0)	
Traumatology	14 (11.1)	1 (10.0)	
Diabetes mellitus, *n* (%)	39 (31.0)	3 (30.0)	0.99
COPD, *n* (%)	16 (12.7)	0	0.61
Asthma, *n* (%)	3 (2.4)	0	0.99
Chronic liver disease, *n* (%)	25 (19.8)	0	0.21
Smoking, *n* (%)	36 (28.6)	4 (40.0)	0.48
Hematological tumor, *n* (%)	2 (1.6)	0	0.99
Solid tumor, *n* (%)	15 (11.9)	2 (20.0)	0.61
Human immunodeficiency virus, *n* (%)	1 (0.8)	0	0.99
Renal replacement previously to ICU admission, *n* (%)	17 (13.5)	1 (10.0)	0.99
Corticosteroids previously to ICU admission, *n* (%)	14 (11.1)	1 (10.0)	0.99
Immunosuppressants previously to ICU admission, *n* (%)	10 (7.9)	1 (10.0)	0.58
Corticosteroids at CRI suspicion, *n* (%)	44 (34.9)	4 (40.0)	0.74
Parenteral nutrition at CRI suspicion, *n* (%)	17 (13.5)	3 (30.0)	0.17
Propofol at CRI suspicion, *n* (%)	69 (54.8)	8 (80.0)	0.19
Deaths at 30 d of CRI suspicion, *n* (%)	9 (7.1)	0	0.99

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; CVC: Central venous catheter; CRI: Catheter-related infection.

Table 2 Maki and vortexing results to diagnosis catheter tip colonization

	Maki +	Maki -	Total
Vortex +	18	0	18
Vortex -	3	115	118
Total	21	115	136

superior to the Maki method[9]. However, this study did not compare the combined use of the vortexing and Maki techniques with respect to the Maki technique alone for the diagnosis of CTC and CRBSI, and this was the novel aim of our study.

We no found any CTC or CRBSI detected by vortexing technique and not detected by Maki technique. No differences had in the comparison of AUC between the technique of Maki technique and the combination of techniques, between the techniques of Maki and vortexing, and between the vortexing technique and the combined techniques for the diagnosis of CTC or CRBSI. Thus, the novel finding of our study was that the use of vortexing combined with the Maki technique did not add any cost-effectiveness for the diagnosis of CTC or CRBSI.

Table 3 Maki and vortexing results to diagnosis catheter-related bloodstream infection

	Maki +	Maki -	Total
Vortex +	9	0	9
Vortex -	1	126	127
Total	10	126	136

Recent guidelines suggest similar recommendation strength and evidence quality for the techniques of Maki and vortexing for the diagnosis of CRI[10,11]. We think that the Maki technique remains the standard technique for the diagnosis of CTC and CRBSI due to the findings of our study and those from the study by Bouza *et al*[9], and because of the greater simplicity of the Maki technique; in addition, we think that the technique of vortexing did not provide profitability to the technique of Maki to the diagnosis of CTC and CRBSI due to the findings of our study.

We want to acknowledge that one limitation of our study was that we have not carried out other quantitative techniques (as sonication or flushing) to compare the profitability of all of them for the diagnosis of CTC and CRBSI. Another limitation of our study was that we have not reported the proportion of CVC excluded (because we did not have complete information on culture with Maki technique, culture with vortexing technique and blood culture). Another limitation of our study was the relatively low number of patients; however, our study showed that to add vortexing technique to Maki technique for the diagnosis of CTC or CRBSI do not apport any benefit due to none of them were detected only by vortexing technique and there were no differences in the AUC when vortexing technique was added to Maki technique.

CONCLUSION

The novel finding of our study was that the combined use of vortexing and Maki techniques did not provide profitability to the technique of Maki alone to CRBSI diagnosis.

ARTICLE HIGHLIGHTS

Research background

A previous study compared the vortexing and the Maki techniques for the diagnosis of catheter-related bloodstream infection (CRBSI), and concluded that vortexing was not superior to the Maki method.

Research motivation

The above study did not compare the combined use of vortexing and Maki with respect to the Maki technique alone for the diagnosis of catheter tip colonization (CTC) and CRBSI.

Research objectives

To determine whether the combined use of vortexing and Maki techniques provide profitability to the Maki technique alone for the diagnosis of CTC and CRBSI.

Research methods

Observational and prospective study. We included patients admited in one Intensive Care Unit that had suspicion of catheter-related infection (CRI) and with one central venous catheter for at least 7 d. The area under the curve (AUC) of the Maki technique, the vortexing technique and the combination of both techniques for the diagnosis of CTC and CRBSI were compared.

Research results

We included 136 episodes of suspected CRI. We found 21 episodes of CTC and 10 episodes of CRBSI. Of the 21 episodes of CTC, 18 (85.7%) were diagnosed by the techniques of Maki and vortexing, 3 (14.3%) were diagnosed only by the technique of Maki, and none was diagnosed only by the technique of vortexing. Of the 10 episodes of CRBSI, 9 (90.0%) were diagnosed by the techniques of Maki and vortexing, 1 (10.0%) was diagnosed by the technique of Maki alone, and none only by the technique of vortexing. No differences had found in the comparison of AUC between the technique of Maki alone and the combination of techniques for the diagnosis of CTC (P = 0.99) and CRBSI (P = 0.99).

Research conclusions

The novel finding of our study was that the use combined of vortexing and Maki techniques did not provide profitability to the technique of Maki alone to CRBSI.

Research perspectives

To study other quantitative techniques (as flushing) to compare the profitability of all of them for the diagnosis of CTC and CRBSI.

FOOTNOTES

Author contributions: Lorente L conceived, designed and coordinated the study, participated in acquisition and interpretation of data, and drafted the manuscript; Lecuona M, González-Mesa, Oliveras-Roura J, Rosado C, Cabrera P, Casal E, Mora ML and Madueño A participated in acquisition of data; Jiménez A participated in the interpretation of data; all authors revised the manuscript critically for important intellectual content, made the final approval of the version to be published and were agreed to be accountable for all aspects of the work.

Institutional review board statement: The Institutional Board of Hospital Universitario de Canarias (San Cristóbal de La Laguna) approved the study protocol.

Clinical trial registration statement: This study is registered at https://www.clinicaltrials.gov/. The registration identification number is NCT06216184.

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ORCID number: Leonardo Lorente 0000-0003-4902-4065; Maria Lecuona Fernandez 0000-0002-7388-4842; Adriana González-Mesa 0000-0002-6882-2786; Judith Oliveras-Roura 0000-0001-9468-9141; Cristina Rosado 0009-0003-0205-1688; Pablo Cabrera 0009-0005-8143-0807; Emma Casal 0009-0000-5616-4109; Alejandro Jiménez 0000-0001-8732-2616; María Luisa Mora 0000-0001-5361-1727; Ana Madueño 0000-0002-6181-4417.

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SYSTEMATIC REVIEWS

Systematic review with expert consensus on use of extracorporeal hemoadsorption in septic shock: An Indian perspective

Yatin Mehta, Abdul Samad Ansari, Amit Kumar Mandal, Dipanjan Chatterjee, Gauri Shankar Sharma, Prachee Sathe, Purvesh V Umraniya, Rajib Paul, Sachin Gupta, Vinod Singh, Yogendra Pal Singh

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Yatin Mehta, Institute of Critical Care and Anesthesiology, Medanta The Medicity, Gurgaon 122001, Haryana, India

Abdul Samad Ansari, Department of Critical Care, Nanavati Max Super Specialty Hospital, Mumbai 400065, India

Amit Kumar Mandal, Department of Pulmonology, Sleep and Critical Care, Fortis Hospital, Mohali, Punjab, Mohali 160062, Punjab , India

Dipanjan Chatterjee, Department of Cardio-Puimonary Critical Care, Medica Superspecialty Hospital, Kolkata 700099, India

Gauri Shankar Sharma, Department of Critical Care Medicine, Fortis Hospital, New Delhi 110070, India

Prachee Sathe, Department of Critical Care Medicine, D.Y. Patil Medical College, Sant Tukaram Nagar, Pimpri Colony, Pimpri-Chinchwad,, Pune 411018, India

Purvesh V Umraniya, Department of Critical Care Medicine, Bhailal Amin General Hospital, Vadodara 390003, Gujarat, India

Rajib Paul, Department of Internal Medicine, Apollo Hospitals, Jubilee Hills, Hyderabad 500 033, India

Sachin Gupta, Department of Anaesthesiology, Narayana Superspeciality Hospital, Gurugram 122002, India

Vinod Singh, Department of Critical Care Medicine, Institute of Critical Care Medicine, Hospital Name - Sir Ganga Ram Hospital, New Delhi 110001, India

Yogendra Pal Singh, Department of Critical Care Medicine, Max Super Speciality Hospital, Delhi 110092, India

Corresponding author: Yatin Mehta, DNB, MD, Chairman, Doctor, Institute of Critical Care and Anesthesiology, Medanta The Medicity, Gurgaon 122001, Haryana, India.
yatinmehta@hotmail.com

Abstract

BACKGROUND

Septic shock is a severe form of sepsis characterised by deterioration in circulatory and cellular-metabolic parameters. Despite standard therapy, the outcomes are poor. Newer adjuvant therapy, such as CytoSorb® extracorporeal haemoadsorption device, has been investigated and shown promising outcome. However, there is a lack of some guidance to make clinical decisions on the use of CytoSorb® haemoadsorption as an adjuvant therapy in septic shock in Indian Setting. Therefore, this expert consensus was formulated.

AIM

To formulate/establish specific consensus statements on the use of CytoSorb® haemoadsorption treatment based on the best available evidence and contextualised to the Indian scenario.

METHODS

We performed a comprehensive literature on CytoSorb® haemoadsorption in sepsis, septic shock in PubMed selecting papers published between January 2011 and March 2023 2021 in English language. The statements for a consensus document were developed based on the summarised literature analysis and identification of knowledge gaps. Using a modified Delphi approach combining evidence appraisal and expert opinion, the following topics related to CytoSorb® in septic shock were addressed: need for adjuvant therapy, initiation timeline, need for Interleukin -6 levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and management flowchart. Eleven expert members from critical care, emergency medicine, and the intensive care participated and voted on nine statements and one open-ended question.

RESULTS

Eleven expert members from critical care, emergency medicine, and the intensive care participated and voted on nine statements and one open-ended question. All 11 experts in the consensus group (100%) participated in the first, second and third round of voting. After three iterative voting rounds and adapting two statements, consensus was achieved on nine statements out of nine statements. The consensus expert panel also recognised the necessity to form an association or society that can keep a registry regarding the use of CytoSorb® for all indications in the open-ended question (Q10) focusing on "future recommendations for CytoSorb® therapy".

CONCLUSION

This Indian perspective consensus statement supports and provides guidance on the use of CytoSorb® haemoadsorption as an adjuvant treatment in patients with septic shock to achieve optimal outcomes.

Key Words: Consensus; CytoSorb; Cytokine; Hemoadsorption; Refractory; Sepsis; Septic shock

Core Tip: This evidence-based expert consensus statement gives information/clarity on the key areas of knowledge gaps of CytoSorb® therapy: need for adjuvant therapy, initiation timeline, need for Interleukin -6 levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints, and (therapy) management flowchart. This expert consensus statements provides general physicians, emergency care physicians, anaesthetist, and intensivists with current information regarding the use of CytoSorb® haemoadsorption as an adjuvant treatment in patients with refractory septic shock.

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INTRODUCTION

Sepsis is described as potentially fatal organ dysfunction induced by an unbalanced host response to infection[1]. Septic shock, on the other hand, is a subset of sepsis in which the underlying circulatory and cellular metabolic abnormalities are severe enough to significantly increase mortality[1]. Sepsis and Septic shock are leading health related issues. The global incidence of sepsis is estimated to be 489 million and sepsis related deaths to be 110 million worldwide, with higher burden in developing countries[2]. India has a higher death rate from sepsis than other South Asian countries[2]. It is estimated that sepsis death rate in India is 213 per 100000 population[2].

The pathophysiology is multifaceted, with both pathogenic and host factors pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) playing a significant part in its progression and subsequent outcome[2,3]. However, the diversity of septic shock requires to accurately characterise individuals, which makes clinical intervention challenging[3,4]. The backbone of treatment remains appropriate and timely antibiotic

therapy, source control, if necessary, IV fluids and titrated vasopressors[5]. However, when these treatment efforts fail to improve the patients' condition in a subset of patients, adjuvant therapies are usually explored to enhance outcomes[5-7].

Despite clinical research efforts and the development of sepsis management guide-lines over the last few decades, the potential to improve the outcome of the condition tends to be limited[8]. Newer adjuvant therapies, such as the targeted elimination of pathogen-associated toxins and mediators by specific adsorption, are gaining recognition[6,7,9]. The use of an extracorporeal haemoadsorption device called CytoSorb® (Cyto-Sorbents corp, New Jersey, United States) for cytokine adsorption is one of the more recent adjuvants. It contains specially designed polymer beads with a large adsorption surface and an adsorption spectrum up to around 60 kDa. It is a high flow, low resistance cytokine adsorbent[7]. CytoSorb extracorporeal haemoadsorption therapy tends to restore the balance of the immune response to infection by eliminating the triggers for the response and the excessive cytokines produced, with the target of achieving immunological homeostasis in patients with severe cytokinemia, including septic shock[4].

Although, there is a substantial amount of clinical data from case series and prospective/retrospective research[10-12] that supports the likelihood of improving treatment outcomes with CytoSorb® hemoadsorption in septic shock, the limited evidence from randomised clinical trials[7] makes it difficult to endorse or adopt in management guide-lines. Furthermore, published evidence on proper patient selection, timing and dosing of CytoSorb® therapy is still scarce. So, there is lack of a consensus guidance to make clinical decisions on the use of CytoSorb® haemoadsorption as an adjuvant in the management of septic shock. Our aim/objectives were to formulate/establish specific consensus statements on the use of CytoSorb® haemoadsorption treatment based on the best available evidence and contextualised to the Indian scenario. Firstly, this Indian consensus provides statements on the use of haemoadsorption as an adjuvant therapy in patients with sepsis. This expert consensus statements provides general physicians, emergency care physicians, anaesthetists, and intensivists with current information regarding the use of haemoadsorption as an adjuvant treatment in patients with refractory septic shock. Secondly, this Indian perspective consensus statement supports use of haemoadsorption as an adjuvant treatment in patients with septic shock and provides guidance to achieve better outcomes. Thirdly, it may also contribute to the optimization of refractory septic shock treatment in India.

MATERIAL AND METHODS

This consensus statement was intended for a target audience of healthcare professionals/clinicians representing/working in the intensive care units/critical care units and emergency departments.

Consensus statement development

Members of the scientific panel conducted a comprehensive literature review on the use of CytoSorb® haemoadsorption in patients with sepsis, septic shock, or who were critically ill in PubMed selecting papers published between January 2011 and March 2023 2021 in English language.The following keywords and terms were use (("cytosorb"[All Fields] OR "cytosorbents"[All Fields] OR "hemoadsorption"[All Fields] OR (("extracorporal"[All Fields] OR "extracorporally"[All Fields] OR "extracorporeal"[All Fields] OR "extracorporeally"[All Fields]) AND ("blood purif"[Journal] OR ("blood"[All Fields] AND "purification"[All Fields]) OR "blood purification"[All Fields]))) AND (("shock"[MeSH Terms] OR "shock"[All Fields] OR "shocked"[All Fields] OR "shocking"[All Fields] OR "shocks"[All Fields]) AND ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND "septic"[All Fields] AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]))) AND ((fha[Filter]) AND (2011/1/1:2023/3/30[pdat])).

The results of a PubMed and Medline database search using suitable Mesh and search keywords yielded a reference list of CytoSorb® publications. A total of 99 papers were identified with no duplicates, and, as a first step, no papers were excluded for other reasons (PRISMA flow diagram reported in Figure 1). As a second step, we excluded papers that were not pertinent to any of the following criteria: (1) Cytosorb and Sepsis/septic shock; (2) Clinical studies/ trials of Cytosorb; and (3) Literature review or systematic reviews of extracorporeal hemoadsorption. According to the selection criteria, out of the 99 results of PubMed research assessed for eligibility, 25 studies were included, out of which 11 clinical trials of Cytosorb were included in final analysis from Pubmed as evidence. In addition, few cross references and 11 references from Cytosorb Product information website was included.

The statements for a consensus document were developed based on the summarised literature analysis and identification of knowledge gaps. A total of nine consensus question statements focused on the use of CytoSorb® therapy in septic shock were formulated. One question was kept open-ended for discussion.

Consensus expert group

The scientific panel convened a consensus expert group of 11 members, each with more than 20 years of expertise in emergency medicine or critical care medicine. These individual experts from India's various geographical cities (Gurugram, Mumbai, Mohali, Kolkata, Delhi, Pune, Vadodara, and Hyderabad) were invited for voting and to express their expert opinion in the consensus process.

Consensus process

The Delphi procedure gathers a group of experts for decision making through an iterative series of questions, anonymous responses, and controlled feedback to the respondents[13]. Using a modified Delphi approach, involving combination of scientific evidence appraisal and expert opinion based on clinical experience of the consensus members, the following topics related statements to CytoSorb® in refractory septic shock were addressed to achieve consensus: need for adjuvant

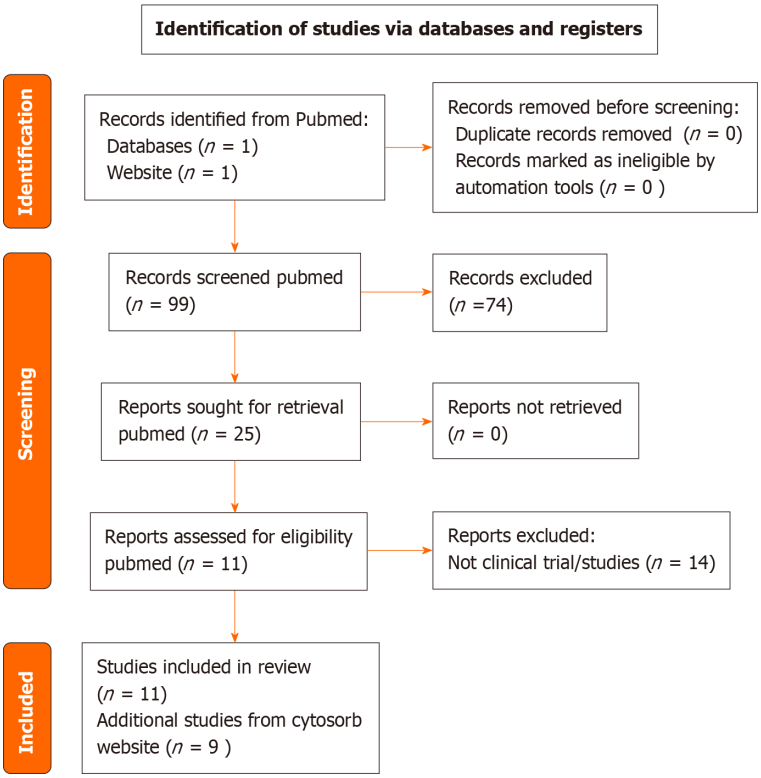

Figure 1 PRISMA flow diagram.

therapy, initiation timeline, need for Interleukin-6 levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and (therapy) management flowchart.

The consensus expert members were asked to vote on all of the statements (agree/yes, disagree/no, or abstain) based on their clinical experience and scientific evidence appraisal obtained from systematic review. They were also asked to offer feedback on the content and/or phrasing of the statements, as well as to suggest any new statements they thought would be beneficial.

Consensus was reached for a particular statement when there was at least 80% agreement in the voting. Statements with no consensus (less than 80% agreement), statements with consensus but relevant remarks that resulted in paraphrasing, and additional statements suggested by experts were reformulated and presented for voting in subsequent modified Delphi rounds. To achieve a decision, maximum three modified Delphi voting rounds were held. The total number of consensuses achieved were calculated.

RESULTS

All 11 experts in the consensus group (100%) participated in the first, second and third round of voting and commenting for the consensus statements.

In the first round, consensus was obtained in 8 (Q1- Q8) of the 9 selected initial statements, whereas consensus was not reached in 1 statement (Q9). It was discussed and re-posted for the second round of voting and comments. Furthermore, 1 statement (Q8) with consensus had positive comments that prompted a modest revision of the phrases. This revised statement Q8 was sent out again along with Q9 for the second round of voting. The one revised statement (Q8) obtained consensus in the second round of voting. For the last statement (Q9, flowchart) agreement was reached in the third round of voting after therapy timelines were modified (Figure 2). Overall, consensus was reached in all nine out of nine statements (Table 1).

The consensus expert panel also recognised the necessity to form an association or society that can keep a registry regarding the use of CytoSorb® for all indications in the open-ended question (Q10) focusing on "future recommendations for CytoSorb® therapy". The potential of this treatment for treating a variety of clinical disorders and its impact on patient outcomes will be better understood with the aid of this registry.

Summary of consensus statements

Q1: Is there a need for adjuvant therapy in the management of refractory septic shock patients when standard of care is insufficient?

Expert panel agreement: A total of 90.91% experts agreed on the need for adjuvant therapy in the management of refractory septic shock patients. (Consensus Achieved).

Table 1 Consensus statement and summary of overall agreement

Questions	Responses, *n* = 11 (%)		Consensus status - overall agreement
	Agreed/yes (%)	Disagreed/no (%)	
Q1. Is there a need for adjuvant therapy in the management of refractory septic shock patients, when standard of care is insufficient?	10 (90.91)	1 (9.09)	A total of 90.91% experts agreed on the need for adjuvant therapy in the management of refractory septic shock patients, when the standard of care is insufficient. (Consensus Achieved)
Q2. In case of refractory septic shock cycle, CytoSorb® ideally be initiated within a maximum of 24 h after diagnosis and start of standard therapy	11 (100)	0 (0)	All experts (100%) agreed that in refractory septic shock cycle, CytoSorb® ideally be initiated within a maximum of 24 h after diagnosis and start of standard therapy. (Consensus Achieved)
Q3. IL-6 levels are not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients	10 (90.91)	1 (9.09)	A total of 90.91% experts agreed that IL-6 levels are not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved)
Q4. There are patients who may require more than one CytoSorb® adsorber to achieve sufficient haemodynamic stabilization	10 (90.91)	1 (9.09)	A total of 90.91% experts agreed that there are patients who may require more than one CytoSorb® adsorber to achieve sufficient haemodynamic stabilization. (Consensus Achieved)
Q5. If you want to continue with CytoSorb® therapy, the absorber should be changed after 6-24 h depending on the clinical course and the machine type availability	11 (100)	0 (0)	All experts (100%) agreed that if CytoSorb® therapy is continued, the absorber should be changed after 6-24 h depending on the clinical course and the machine type availability. (Consensus Achieved)
Q6. CytoSorb® therapy is generally a safe therapy	10 (90.91)	1 (9.09)	A total of 90.91% experts agreed that CytoSorb® is generally a safe therapy. (Consensus Achieved)
Q7. Sepsis-induced AKI requiring RRT is no prerequisite to initiate CytoSorb® therapy in refractory septic shock patients	11 (100)	0 (0)	All experts (100%) agreed that sepsis-induced AKI requiring RRT is not a prerequisite to initiate CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved)
Q8. Evaluation of the efficacy of CytoSorb® therapy should be based on more proximal endpoints like haemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality	10 (90.91)	1 (9.09)	A total of 90. 91% experts agreed that the evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like haemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality. (Consensus Achieved)
Q9. Do you think this flowchart can be helpful to a doctor very new to the therapy to ensure a certain level of best practice?	11 (100)	0 (0)	All experts (100%) agreed on the (revised) flowchart for doctor who are new to the therapy to ensure a certain level of best practice. (Consensus Achieved)

AKI: Acute kidney injury; RRT: Renal replacement therapy.

Reason/scientific evidence: Standard of care in septic shock with the cornerstones of source control and fluid and catecholamine therapy is of unquestionable importance, however, not directly addressing the dysregulated immune response as a central problem. Especially in refractory patients, with no adequate response to standard therapy measures, adjuvant approaches might be needed and be able to fill this therapeutic gap. Consequently CytoSorb® haemoadsorption treatment attempts to restore the balance of the immune response to infection by eliminating some triggers for the response and the excessive cytokines produced, with the target of achieving immunological homeostasis[4,7,14]. It has the capacity to disrupt the immune response at various stages by eliminating various inflammatory mediators like PAMPs, DAMPs and cytokines from blood, thereby directly addressing the problem of the dysregulated host response.

Q2: In case of refractory septic shock cycle, CytoSorb® haemoadsorption should ideally be initiated within a maximum of 24 h after diagnosis and start of standard therapy.

Expert panel agreement: All experts (100%) agreed that in refractory septic shock, CytoSorb® should ideally be initiated within a maximum of 24 h. (Consensus Achieved).

Reason/scientific evidence: Kogelmann *et al*[15] presented a dynamic scoring system to support patient selection for CytoSorb® therapy in early refractory septic shock. Among other things analysis of nearly 200 patients treated with CytoSorb® in septic shock revealed that those treated within the first 24 h had a higher chance of surviving than those treated after 24 h, and for every hour of CytoSorb® haemoadsorption treatment delay, the risks of death at Day 56 increased by 1.5% ($P < 0.034$). These positive findings are in line with various other publications, like data from Singh *et al*[16] and Paul *et al*[17], in which CytoSorb® therapy was shown to be a safe and well tolerated rescue therapy which should be used preferably within the first 24 h after onset of septic shock. Approaches in which CytoSorb® therapy was initiated in selected refractory patients within the first 24 h of onset of septic shock or start of standard therapy respectively showed positive effects with regard to improved hemodynamic stabilization and signals for improved survival[12].

Q3: IL-6 level is not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients.

Expert panel agreement: A total of 90.91% experts agreed that IL-6 level is not a mandatory parameter to decide on using CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved).

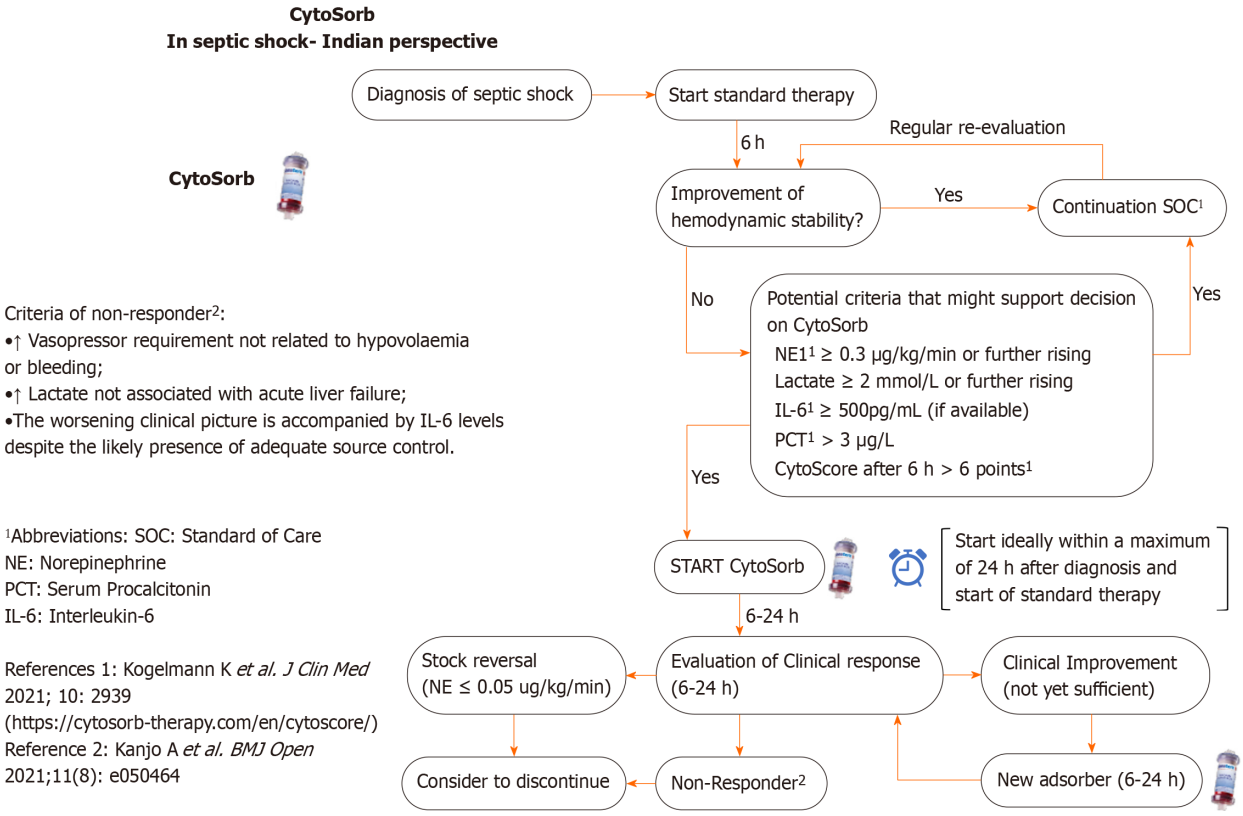

Figure 2 Flowchart.

Reason/scientific evidence: Although IL-6 levels are a promising target due to its involvement in the pathogenesis of septic shock, the profile of IL-6 kinetics in critically ill patients may be heterogeneous and influenced by a number of factors. Furthermore, IL-6 levels alone may not be especially predictive of the patient's future reaction[4]. Addition-ally, from a practical perspective IL-6 levels might not be available in a timely manner in every center. Various clinical studies have shown good results with CytoSorb® therapy when patient selection was not based on IL-6 levels, but rather the clinical picture of (refractory) septic shock with elevated (and increasing) levels of vasopressor needs and other criteria[7,12,18]. In the light of all this it was decided that measuring IL-6 levels before initiating CytoSorb® treatment for refractory septic shock was NOT mandatory.

Q4: There are patients who may require more than one CytoSorb® adsorber to achieve sufficient hemodynamic stabilization.

Expert panel agreement: A total of 90.91% experts agreed that there are patients who may require more than one CytoSorb® adsorber to achieve sufficient hemodynamic stabilization (Consensus Achieved).

Reason/scientific evidence: In a systematic review and meta-analysis, Hawchar *et al*[10] examined the role of haemoadsorption using CytoSorb® in attaining quick haemo-dynamic stabilisation in patients with refractory vasoplegic shock. The available data demonstrated that early CytoSorb® therapy resulted in a considerable reduction in vasopressor (norepinephrine) need following treatment (median from 0.55 µg/kg/min to 0.09 microg/kg/min, $P < 0.001$), which indicates the important contribution of early haemoadsorption in achieving rapid haemodynamic stabilization in patients with refractory vasoplegic shock[10]. Rugg *et al*[12] could improve haemodynamic stabilization with only one adsorber having been used in the majority of the patients. Friesecke *et al*[19] on the other hand utilized a mean of 3 ± 1.5 CytoSorb® adsorbers per patient when they conducted a prospective clinical study in twenty patients with refractory septic shock. Also, in this research, CytoSorb® therapy had favorable outcomes and resulted in a considerable reduction in vasopressor (noradrenaline) needs as well as an increase in lactate clearance. Shock reversal was achieved in 65% (n = 13) of the patients[19]. So, in conclusion the number of adsorbers needed might vary from patient to patient and there are patients who may require more than one CytoSorb® adsorber to achieve sufficient haemodynamic stabilization.

Q5: If you want to continue with CytoSorb® therapy, the adsorber should be changed after 6-24 h depending on the clinical course and the machine type availability.

Expert panel agreement: All experts (100%) agreed that if CytoSorb® therapy is continued, the adsorber should be changed after 6-24 h depending on the clinical course and the machine type availability. (Consensus Achieved).

Reason/scientific evidence: According to the current instructions for use (IFU)[20], one adsorber can stay for up to 24 h on a patient. Recent experiences however suggest that some patients seem to benefit from earlier changes of the adsorber *i.e.*, after 12 h or even earlier. Back in April 2020 the United States (US) Food and Drug Administration's (FDA) Emergency Use Authorization had been granted for CytoSorb® extracorporeal blood purification treatment to reduce hyperinflammation in seriously ill coronavirus disease 2019 (COVID-19) patients[21]. An FDA-specific dose of 12:12:24:24

h had to be used in these patients. Hayanga *et al*[21] retrospectively analysed the data from a US CytoSorb® Therapy in COVID-19 (CTC) Registry. The analysis showed that CytoSorb® treatment was linked with improved survival rates in critically ill COVID-19 patients who received extracorporeal membrane oxygenation. Earlier changes might ensure an ongoing high removal capacity of the adsorber avoiding early saturation in situation with a high cytokine load for the device[22]. Therefore, a change of adsorber might be appropriate anytime between 6-24 h. It was discussed that it does not need to be changed earlier than 6 h as the device would work properly but a change should not occur later than 24 h to comply with the current IFU, also as no significant removal capacity beyond this point should be expected from the adsorber. As usual, the exact timing of adsorber changes (if applicable) would vary from patient to patient.

Q6: CytoSorb® therapy is generally a safe therapy.

Expert panel Agreement: A total of 90.91% experts agreed that CytoSorb® is generally a safe therapy. (Consensus Achieved).

It was also acknowledged that as with all other therapeutic measures even CytoSorb® has its own side effects, but it is generally a safe therapy.

Reason/scientific evidence: To date CytoSorb® therapy has been used in a wide variety of critically ill patients[23]. Features like size-selectivity and concentration dependency as well as the high biocompatibility support a favourable safety profile of the device, which was further supported by various publications[23].

Diab *et al*[24] conducted a multicenter randomized controlled trial of CytoSorb therapy in patients undergoing surgery for infective endo carditis (REMOVE trial). A total of 288 patients were randomly allocated to either intraoperative CytoSorb® hemoadsorption (n = 142) or control (n = 146). Apart from the effect on postoperative organ dysfunction, the trial also investigated the safety profile in the two groups, which included peri-operative complications and adverse events[24]. The trial found that the frequency and pattern of postoperative complications and adverse events (distributive shock, acute renal dysfunction, respiratory insufficiency, re-exploration for bleeding, central nervous system related, and cardiac events) were comparable in both groups, confirming the safety of this device[24].

The results of the Eleventh analysis of registry data from an International CytoSorb® Registry conducted by Hawchar *et al*[25] further supported the favourable safety profile of CytoSorb® therapy. Data from 1434 critically ill patients (sepsis/septic shock (65.3%), cardiac surgery perioperatively (11.9%), cardiac surgery postoperatively (4.7%), and other (18.1%) indications) from 46 centres revealed that CytoSorb® treatment related complications (cardiac, respiratory, blood, central nervous, and kidney related) were re-ported in only 2.16% (n = 31) patients, whereas the majority of patients (97.8%, n = 1403) had no reported CytoSorb® treatment-related complications[25]. They concluded that in line with all other papers published so far, regardless of the type of the study or case report, the 11th analysis of the Registry data further suggests that CytoSorb® therapy is safe[25]. So, despite acknowledging that, like any other therapeutic interventions, CytoSorb® can also have adverse effects, *e.g.*, with regard to unwanted drug removal or complications associated with the extracorporeal circuit, the therapy was regarded as generally safe.

Q7: Sepsis-induced acute kidney injury (AKI) requiring renal replacement therapy (RRT) is no prerequisite to initiate CytoSorb® therapy in refractory septic shock patients.

Expert panel agreement: All experts (100%) agreed that sepsis-induced AKI requiring RRT is not a prerequisite to initiate CytoSorb® therapy in refractory septic shock patients. (Consensus Achieved).

Reason/scientific evidence: CytoSorb® therapy is a haemoadsorption therapy targeting small and middle-sized hydrophobic substances. This is in contrast to the classical hydrophilic targets of RRT. Circuits from renal replacement systems can be used technically for integration of the CytoSorb® adsorber, however, in principle the decision for or against CytoSorb® should be made independent of the indication and start of continuous renal replacement therapy or other extracorporeal therapies as one cannot replace the other[26].

Hawchar *et al*[7] conducted a prospective, randomised pilot study of CytoSorb® as a stand-alone therapy in patients with septic shock in Hungary. Twenty (n = 20) patients with septic shock of medical origin, on mechanical ventilation, norepinephrine > 10 μg/min, procalcitonin > 3 ng/mL, but no requirement for RRT were included in this proof-of-concept trial and were randomised into CytoSorb® (n = 10) and Control (n = 10) groups[7]. Over the assessed time-points, vasopressor (norepinephrine) requirements and procalcitonin levels decreased significantly in the CytoSorb® group compared to the control group (P < 0.05)[7].

If early need for RRT due to sepsis-induced AKI crises, integration of CytoSorb® into the circuit can still be easy, however waiting for an RRT indication shouldn't delay the start of CytoSorb® when appropriate to address hyperinflammation and ongoing haemo-dynamic instability in early refractory septic shock. Therefore, sepsis-induced AKI requiring RRT was NOT seen as a prerequisite to initiate CytoSorb® therapy in these patients.

Q8: Evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like haemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality.

Expert panel agreement: A total of 90.91% experts agreed that the evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like haemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function instead of mortality. (Consensus Achieved).

Reason/scientific evidence: Sepsis is a syndrome and not a disease and septic shock is a disorder with a diverse phenotype. First of all, CytoSorb® therapy is not a primary therapy to treat sepsis, but only an adjunctive option to address the dysregulated immune response as an underlying problem in septic shock patients. So CytoSorb® is solely used to eliminate cytokines (and other mediators) and decrease the complications of a dysregulated host response[8]. Thus, objective assessment of CytoSorb® in septic shock is challenging. Furthermore, the reason for mortality in septic shock patients may be multifunctional and not directly attributable to the host response, which can lead to overestimation of syndrome-attributable risks[27].

Various endpoints such as haemodynamic stabilisation, improvement in organ function or inflammatory biomarkers, and survival have been recorded in studies with CytoSorb® in sepsis/septic shock[7,8,10,19]. Understanding the complexity of the syndrome, assessment of the efficacy of CytoSorb® treatment in studies should be based on the complexities of critical illness syndromes with endpoints such as haemodynamic stability, inflammatory biomarkers, and/or improvement in organ function rather than mortality.

Q9: Do you think this flowchart can be helpful to a doctor very new to the therapy to ensure a certain level of best practice?

Expert panel disagreement: initially but all experts (100%) agreed on the revised flowchart for doctors new to therapy. (Consensus Achieved).

Reasons: Based on the following discussion, the original flowchart was revised and the revised flowchart was agreed upon (see Figure 2).

Suggested modifications in original flowchart: (1) Changing the time period to change the adsorber from the 12 h specified in the chart to 6-24 h based on clinical criteria; (2) The flowchart should preferably be modified to contain three distinct pathways for patients who were significantly improving, slightly improving, and not at all improving; and (3) For the benefit of physicians with less experience in this area, it may also be necessary to mention the potential criteria for starting therapy with inclusion of the CytoScore[15] definition along with therapy flow chart.

Q10: Future recommendations for CytoSorb® therapy (Open ended discussion and not for voting).

Recommendation: To establish an association/society that can maintain a registry on the utilization of CytoSorb® in the management of different indications. This will help to get valuable real-world evidence data about the potential of this therapy in multiple clinical conditions and its effect on patient outcomes.

DISCUSSION

Septic shock occurs from a dysfunctional host response to infection, resulting in a state described as a "cytokine storm" that progresses to shock and carries the high risk of development of a multi organ dysfunction syndrome[1,28]. The standard therapy is timely resuscitation, antibiotics, and targeted vasopressors[5]. Despite standard therapy, a certain subset of individuals have poor outcomes and require adjuvant therapy[5]. To improve outcomes, various innovative adjuvant therapies have been explored. Blood purification treatments, such as high-volume continuous haemofiltration or cytokine and/or endotoxin elimination, have been proposed as one such strategy to promote immune homeostasis[4].

Sorbent technologies have recently garnered a lot of consideration. CytoSorb® based haemoadsorption is one such therapy. The CytoSorb® device is composed of biocompatible, extremely porous polymer beads[7,20,24]. The adsorber has a surface area of around 45000 m^2 compared to a standard hemofilter with a surface area of 1-1.5 m^2 and a molecular cut-off of approximately 60 kDa for eliminating cytokines as well as other hydrophobic substances. As a result, CytoSorb® does not adsorb endotoxin with a molecular weight of 100 kDa[4,7,20,29]. CytoSorb® has been developed and approved for treatment in patients with severe cytokinemia, but can also adsorb bilirubin, myoglobin, free haemoglobin and the antithrombotics ticagrelor and rivaroxaban during cardiopulmonary bypass[24]. Studies have revealed favorable results in patients with sepsis and septic shock, with, however, only limited evidence from randomized control trials[7,10,11,12,17,28].

In this consensus paper, an attempt was made to address the utilization and adoption of CytoSorb based haemoadsorption therapy in patients with septic shock with critical appraisal of the evidence from the current available literature. This consensus statement gives more information/clarity on the key areas of knowledge gaps of CytoSorb® therapy: Need for adjuvant therapy, initiation timeline, need for Interleukin -6 levels, duration of therapy, change of adsorbers, safety, prerequisite condition, efficacy endpoints and (therapy) management flowchart. Table 2 summarizes the consensus statement. The current consensus statements are based on existing literature data, primarily from case series, prospective/retrospective studies, and limited randomised trials. These statements also augment subject experts' opinions/views based on their clinical expertise and resource settings.

These consensus statements are intended to offer guidance to clinicians working in the field of critical care/ emergency care, healthcare manager, healthcare organizations and patients regarding the use of CytoSorb® in septic shock.

We expect that this expert agreement will facilitate the personalized, safe, and pragmatic use of CytoSorb® haemoadsorption in septic shock patients in the critical care setting. Knowledge always lags behind evidence, and this expert consensus has shortcomings that we intend to resolve in future.

The consensus statement has both strengths and limitations

Major strengths: (1) Being the first sort of consensus statement that provides information and guidance on the use of CytoSorb® therapy in critically ill/septic shock patients in India; (2) involving a significant group of experts from various geographical cities across India with long standing experience in the field of critical care; (3) providing various articles on CytoSorb therapy (based on a systematic review) and critically appraising evidence by sharing it with all participating experts; (4) using a modified Delphi technique with open-ended (text-based) feedback from respondents and subsequent adaptation; and (5) providing of a Flowchart for the Indian market which will help doctors to optimise for the use of CytoSorb® therapy in septic shock patients.

Limitations: Although the majority of the publications critically evaluated after the systematic review were research studies, case series, and systematic reviews, there is substantially less evidence from randomised control trials.

Table 2 Summary of consensus statements

Number	Summary of consensus statements
1	There is the need for adjuvant therapy (CytoSorb® haemoadsorption) in the management of refractory septic shock patients, when the standard of care is insufficient
2	In refractory septic shock cycle, CytoSorb® ideally be initiated within a maximum of 24 h after diagnosis and start of standard therapy
3	In the initiation of CytoSorb® therapy in refractory septic shock patient, IL-6 levels are not a pre-requisite or mandatory parameter for decision making
4	In a subset of patients, more than one CytoSorb® adsorber may be required to achieve sufficient haemodynamic stabilization
5	In continuation of CytoSorb® therapy, the absorber should be changed after 6-24 h depending on the clinical course and the machine type availability
6	CytoSorb® therapy is generally a safe therapy
7	Sepsis-induced AKI requiring RRT is not a prerequisite to initiate CytoSorb® therapy in refractory septic shock patients
8	The evaluation of the efficacy of CytoSorb® therapy should be based on endpoints like haemodynamic stabilization, inflammatory biomarkers, and/or improvement in the organ function, instead of mortality
9	The (displayed, Figure 2) flowchart can be helpful to a doctor very new to the therapy to ensure a certain level of best practice

AKI: Acute kidney injury; RRT: Renal replacement therapy.

CONCLUSION

This Indian perspective consensus statement supports and provides guidance on the use of CytoSorb® haemoadsorption as an adjuvant treatment in patients with septic shock to achieve optimal outcomes. We hope that this consensus statement will help in facilitating proper treatment initiation and maintenance of CytoSorb® haemoadsorption therapy in the management of refractory septic shock and it may also contribute to the optimization of refractory septic shock treatment in India.

ARTICLE HIGHLIGHTS

Research background

Septic shock is a severe form of sepsis characterised by deterioration in circulatory and cellular-metabolic parameters. Despite standard therapy, the outcomes are poor. Newer adjuvant therapy, such as CytoSorb® extracorporeal haemoadsorption device, has been investigated and shown promising outcome.

Research motivation

There is a lack of some guidance to make clinical decisions on the use of CytoSorb® haemoadsorption as an adjuvant therapy in septic shock.

Research objectives

To formulate/establish specific consensus statements on the use of CytoSorb® haemoadsorption treatment based on the best available evidence and contextualised to the Indian scenario.

Research methods

We performed a comprehensive literature on CytoSorb® haemoadsorption in sepsis, septic shock in PubMed selecting papers published between January 2011 and March 2023 2021 in English language. The statements for a consensus document were developed based on the summarised literature analysis and identification of knowledge gaps. Using a modified Delphi approach combining evidence appraisal and expert opinion, the following topics related to CytoSorb® in septic shock were addressed and consensus was formulated.

Research results

All 11 experts in the consensus group (100%) participated in the first, second and third round of voting. After three iterative voting rounds and adapting two statements, consensus was achieved on nine statements out of nine statements. The consensus expert panel also recognised the necessity to form an association or society that can keep a registry regarding the use of CytoSorb® for all indications in the open-ended question (Q10) focusing on "future recommendations for CytoSorb® therapy".

Research conclusions

This Indian perspective consensus statement supports and provides guidance on the use of CytoSorb® haemoadsorption as an adjuvant treatment in patients with septic shock to achieve optimal outcomes.

Research perspectives

We expect that this expert agreement will facilitate the personalized, safe, and pragmatic use of CytoSorb® haemoadsorption in septic shock patients in the critical care setting. Knowledge always lags behind evidence, and this expert consensus has shortcomings that we intend to resolve in future.

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FOOTNOTES

Author contributions: Mehta Y, Ansari A, Mandal AK, Chatterjee D, Sharma GS, Sathe P, Umraniya PV, Paul R, Gupta S, Singh VK, and Singh YP contributed to conceptualization/ideation, data analysis; contributed to writing – original draft, writing – review & editing; all the authors have equally contributed towards conceptualization/ideation, data analysis, manuscript review and final approval; all authors have read and agreed to the published version of the manuscript.

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CASE REPORT

Angioinvasive mucormycosis in burn intensive care units: A case report and review of literature

Atul Parashar, Chandra Singh

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Atul Parashar, Chandra Singh, Plastic Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Atul Parashar, MBBS, MCh, MS, Professor, Plastic Surgery, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. atulparashar@hotmail.com

Abstract

BACKGROUND

Mucormycosis is a rare, rapidly progressive and often fatal fungal infection. The rarity of the condition lends itself to unfamiliarity, delayed treatment, and poor outcomes. Diagnosis of fungal infections early enough to enable appropriate treatment occurs in less than half of affected patients.

CASE SUMMARY

An 11-year-old girl with a history of 15% total body surface area scald burns involving both lower limbs progressed to develop angioinvasive mucormycosis. This further led to a thrombosis of the right external iliac artery and vein and rapidly progressive necrosis of surrounding soft tissues. She also had dextrocardia and patent foramen ovale. A right hip disarticulation and serial aggressive debridements were performed but she went on to develop systemic sepsis with multisystem involvement and succumbed to the infection. Pathology revealed mucor species with extensive vascular invasion.

CONCLUSION

This case highlights the importance of maintaining vigilance for mycotic infections and acting appropriately when there are signs of fulminant wound infection.

Key Words: Angioinvasiveness; Mucormycosis; Burn sepsis; Femoral artery thrombosis; Case report

Core Tip: Mucor species are known spread rapidly across fascial tissue planes and cause vascular invasion leading to high mortality rates despite aggressive surgical debridement. There are only rare reports of mucormycosis in burn wounds and most surgeons are not well-versed with its early features. This can lead to delay in diagnosis and institution of appropriate medical and surgical care. We came across one such case at our center recently, which prompted us to conduct a review of available literature on incidence of mucormycosis in burn wounds and available guidelines for management.

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INTRODUCTION

Historically, mycotic infections in burn patients have been rare events. Burn wounds developing fungal infection should alarm the treating physician because of their association with high mortality rates, disabling amputations and prolonged hospital stay[1]. Because of the rarity of the condition, only 15%-40% of patients have been shown to be diagnosed early enough to ensure early appropriate treatment. Even in them, outcomes are poor and mortality remains high. Breach in the continuity of skin by trauma or burn injury may lead to colonization of the wound with fungi from surrounding environment, contaminated dressings *etc.* and this has been postulated to be the most common mechanism for cutaneous mucormycosis. Fungal infections, when occurring in burn wounds, tend to present in the second week or later following burn injury. The classic presentation is black deposits over the burn raw area appearing spontaneously in previously healing wounds[2]. Patients with larger surface area burns are at higher risk for acquiring such infections[3].

Mucor species are known to cause necrosis of adjacent soft tissues, spread rapidly across fascial tissue planes, cause vascular invasion and hematogenous dissemination, leading to mortality rates as high as 100% once disseminated infection has set in. Aggressive surgical debridement is advocated but even with that, survival may not be ensured in most of the victims. Considering there are only rare reports of mucormycosis in burn wounds[4,5], most treating surgeons are not well-versed with its early features. This leads to delay in diagnosis and institution of appropriate medical and surgical care. We came across one such case at our center recently, which prompted us to conduct a review of available literature on incidence of mucormycosis in burn wounds, its pathophysiology, and available guidelines for management. We hereby report our case and review relevant literature to raise awareness about this potentially fatal complication.

After *Aspergillus*, Mucorales fungi are the next common pathogens in patients with hematological malignancy, hematopoietic stem cell transplantation and solid organ transplantation[6,7]. Additionally, Mucorales infections are increasingly recognized in individuals with diabetes mellitus[8], after trauma or iatrogenic injury[9,10] and have been associated with outbreaks following natural disasters[11]. A review of the epidemiology, diagnosis, treatment and outcomes of mucormycosis (then zygomycosis) by Roden *et al*[9] has provided valuable insights into this important invasive fungal disease.

CASE PRESENTATION

Chief complaints

An 11-year-old girl presented to our center with 51-day-old post-burn raw areas over both lower limbs.

History of present illness

The patient had 15% total body surface area burns to begin with. She sustained the scald burn injuries by spillage of hot milk and was initially treated at several local hospitals where she received supportive care, intravenous antibiotics and the raw areas were managed with dressings. Since she had deep dermal wounds, there was no epithelization and she continued with local dressings at various peripheral medical centers. During the 50 d she was managed at three separate local hospitals and as the general condition continued to deteriorate, she was finally referred to our center on post-burn day 51.

History of past illness

She had dextrocardia with small patent foramen ovale. She also had a past history of left common femoral vein thrombosis in her neonatal period which was successfully treated but the underlying etiology was not determined.

Personal and family history

Nothing significant.

Physical examination

On presentation, she had systemic signs of inflammation, high fever, tachycardia and hypotension. Her general condition was poor with post-burn raw areas over the right thigh and groin and left thigh and leg. The right thigh had full thickness involvement over the anteromedial aspect with exposed thigh muscles There was slough and necrosis of surrounding soft tissues (Figure 1A). The left thigh and leg had partially healing raw areas with pale granulation tissue over the anteromedial thigh, extending to the left leg (Figure 1B).

Laboratory examinations

Blood investigations were suggestive of anemia (hemoglobin: 8.1 g%), leukocytosis (total leukocyte count: 73 700) with shift to the left (91% neutrophils), thrombocytopenia (platelets: 7.14 × 10^5), hypoproteinemia (3.3 g/dL) and hypoalbuminemia (1.3 g/dL). Liver and kidney function tests were within normal limits. Wound swab on presentation revealed Gram-negative coccobacilli.

Imaging examinations

At presentation, chest X ray was suggestive of pleural effusion and abdominal ultrasonography revealed mild hepatomegaly. Postoperatively, computed tomography (CT) angiography was performed for bilateral lower limb vessels, which revealed acute thrombosis of the right external iliac artery and non-opacification of the right lower limb major vessels (Figure 2).

FINAL DIAGNOSIS

Angioinvasive mucormycosis.

TREATMENT

The patient was transferred to the burn care unit. Intravenous fluid resuscitation, titrated to adequate urine output and central venous pressure, was administered. Empirical antibiotic therapy based on the burn unit protocol at our center was started. Blood transfusions were given to improve the hemoglobin level. The wound surface slough was excised under intravenous sedation. The patient however continued to have regular fevers and hemodynamic instability. On day 3 of admission, the right lower limb turned pale with absent pinprick. She was moved to the operating room for debridement. Thorough debridement of necrotic muscles and soft tissue was performed and the tissue was sent for bacterial and fungal culture sensitivity. Intraoperative thromboses of the right femoral artery and veins were noted. However, the deeper layer of the muscles was viable with adequate bleeding. Intravenous infusion of heparin, 10 μg/kg/h, was started with activated partial thromboplastin time monitoring.

OUTCOME AND FOLLOW-UP

Intraoperative tissue biopsy showed growth of aseptate hyphae suggestive of *Mucor* species. The patient was started on intravenous liposomal amphotericin B (5 mg/kg). Despite all these measures, soft tissue necrosis rapidly progressed to involve the anterior abdominal wall and perineum over the next 8 h (Figure 3). The patient continued to have high fever and systemic sepsis. Consent for amputation was obtained and right hip disarticulation with external iliac ligation and aggressive debridement of the anterior abdominal wall and perineum were performed (Figure 4).

Postoperatively, in view of severe acidosis, the patient was kept on mechanical ventilation and also required inotropic support. Hemoglobin further fell to 6.8 g% and multiple transfusions were given. The wound condition continued to deteriorate rapidly, and the patient was managed with bedside debridement under sedation because her general condition was considered unfit for anesthesia. The blood oxygenation failed to improve, and metabolic acidosis persisted despite mechanical ventilation. Chest X ray revealed bilateral lung infiltrates. She arrested on day 7 of admission at our center and could not be revived. The cause of death was deemed to be angioinvasive cutaneous mucormycosis infection of the burn wound with hematogenous dissemination and secondary pulmonary invasion leading to systemic sepsis and respiratory failure.

DISCUSSION

Zygomycetes were first reported as a cause of human disease in 1885 by Paltauf[12] but it remained a rare diagnosis with fatal consequences for a long time. The last decade though, has seen their emergence as increasingly important pathogens. This rise in incidence of infection is seen in specific population groups, such as solid organ transplant recipients, diabetics, and patients on deferoxamine therapy[13]. Although still encountered less frequently than other fungal infections such as candidiasis or aspergillosis, these organisms are special because of their disproportionately high propensity to cause life-threatening infections even in patients with no underlying immunodeficiencies or immunosup-

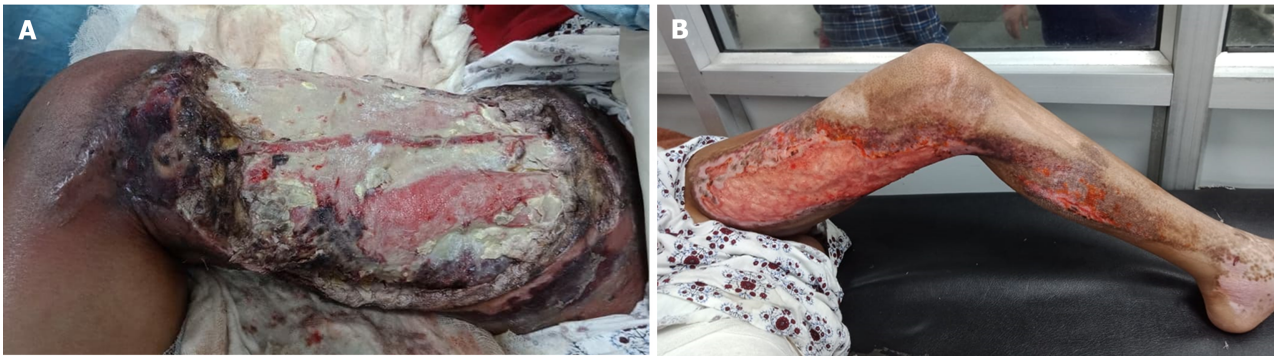

Figure 1 The leg. A: Right thigh raw areas with necrosis of surrounding soft tissues and slough; B: Raw areas over left thigh and leg.

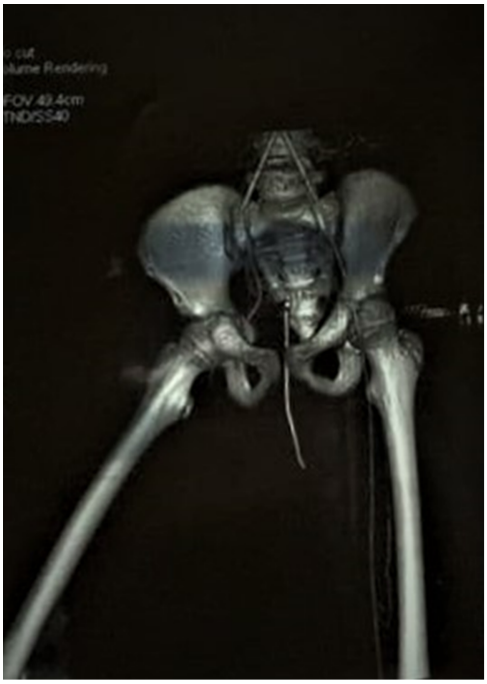

Figure 2 Computed tomography angiography showing non-opacification of the right external iliac artery.

pressive therapy. Roden *et al*[9] conducted a large scale review of all cases of zygomycosis reported in English literature since 1885 and studied a total of 929 cases. They reported an increasing trend in the incidence of these infections and found that 19% of cases had no underlying predisposing condition. Only 1.2% of the cases were reported to be associated with burn injuries. The mortality rate was 64% in this subgroup. Among the others, 44 patients (25%) had associated penetrating trauma and 32 (18%) had undergone surgery. Mortality was lower in these groups at 23% and 38%, respectively. In contrast, the larger majority of patients (81%, n = 753) had associated underlying conditions such as diabetes mellitus (36%), malignancy (17%), solid organ or bone marrow transplantation (12%), desferoxamine therapy (6%), injecting drug use (5%), renal failure (4%), or HIV infection (2%).

The term mucormycosis has been interchangeably used with the term zygomycosis. It is used to describe infections caused by fungi belonging to Zygomycota, a former phylum that has now become obsolete after revision of nomenclature of the kingdom Fungi[14,15]. Now, mucormycosis is used for infections caused by fungi belonging to the order Mucorales, which includes species belonging to the following genera, *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces*. Among these, various reviews have reported *Rhizopus* to be the most common causative pathogen (47%) followed by *Mucor* (14%–18%)[16]. Causative pathogens also vary by geographical region. *Lichthemia* infections are largely reported in Europe (23% *vs* 7%) whereas *Saksenaea* spp. have been reported in isolates from North and South America, India and Australia[16].

These infections occur in patients with disrupted cutaneous barriers, as a result of either traumatic implantation of soil as in road side accidents, burn injuries, contaminated dressings maceration of skin by a moist surface[17-20], or even *via* direct access through intravenous catheters or subcutaneous injections (*e.g.* insulin injections in diabetics)[21-23]. In addition, it has been shown that *Rhizopus* spp. utilize deferoxamine as a siderophore leading to increased pathogenesis in patients on deferoxamine therapy[24,25].

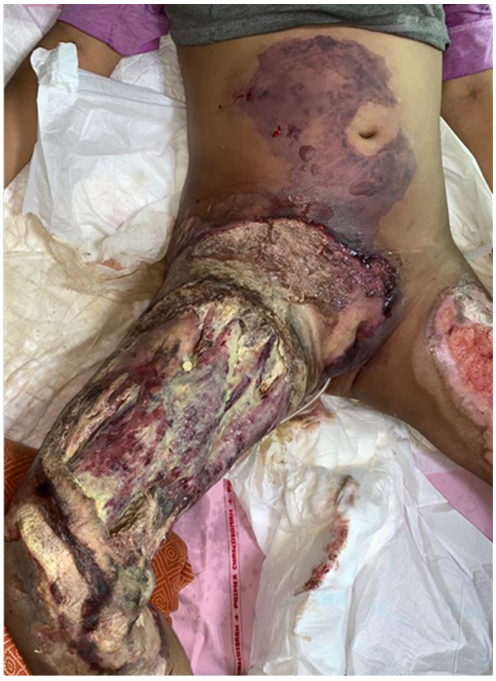

Figure 3 Rapidly progressive necrosis of the anterior abdominal wall.

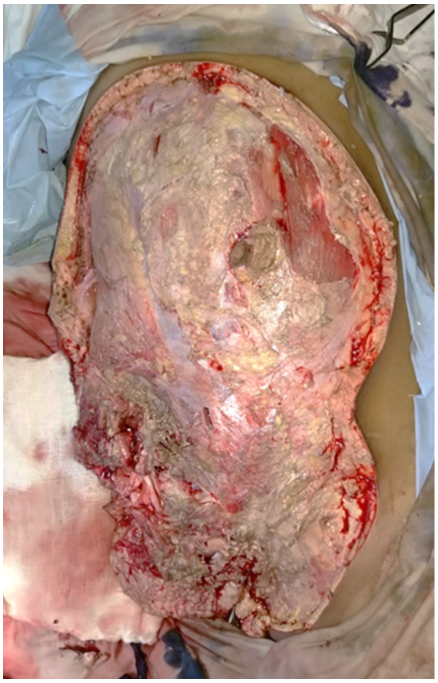

Figure 4 Postoperative wound status after right hip disarticulation and debridement of the anterior abdominal wall and perineum.

Based on sites of involvement, mucormycosis may be grossly divided into six clinical categories, namely rhino-orbital-cerebral (ROC), pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Of these, ROC mucormycosis is the most commonly noted (34%), followed by cutaneous (22%), pulmonary (20%) and disseminated (13%) mucormycosis[26]. Different underlying conditions predispose to specific sites of involvement; for example, ROC mucormycosis is significantly more common in patients with diabetes mellitus (51% *vs* 23%). Cutaneous mucormycosis is more commonly observed in immunocompetent patients with a history of trauma (69% *vs* 11%), and pulmonary mucormycosis is more prevalent in patients with a history of solid organ transplantation and those with neutropenia. Disseminated infection is more frequently seen in patients with underlying hematological malignancy[26].

The skin is reported to be the primary site of involvement in 14%-22% cases of mucormycosis overall[9] and in 27% of cases among children[27,28]. Most of these patients do not have associated neutropenia or underlying predisposing conditions. Instead, disruption of the normal protective cutaneous barrier is present in virtually all cases, followed by

contamination with fungal spores. It is found to be associated with major penetrating trauma in 34% of cases, postsurgical in 33%, after-burn raw areas in 11%, and minor trauma such as cuts and grazes (during gardening *etc*.) in 4%[29,30]. In another review by Jeong *et al*[16], eight of 851 cases were attributed to the use of contaminated dressings, intravenous access sites, or needles[16]. Additionally, Roden *et al*[9] observed female sex and HIV infection to be independent risk factors for cutaneous involvement[9]. In diabetics, cutaneous lesions may arise at subcutaneous insulin injection or catheter insertion sites[22,23]. In cutaneous involvement, the infection may remain limited to the skin or involve the underlying deeper structures, muscles, fascia and even bone. This may lead to necrotizing fasciitis, which has a mortality approaching 80%[31-33]. In 20% of cases it may undergo hematogenous dissemination from the skin to other noncontiguous organs.

Extensive angioinvasion leading to vascular thrombosis and tissue necrosis is a hallmark of mucormycosis on histopathology[26]. The pathogen achieves this by invading and damaging the endothelial cells lining the blood vessels, thereby achieving the ability of hematogenous dissemination from the primary site of infection to other target organs (central nervous system, lungs *etc*.). Incidence of dissemination is noted to be the highest in neutropenic patients with pulmonary mucormycosis. Burn patients are particularly prone to cutaneous disease. After disseminated mucormycosis sets in, it has a high mortality rate approaching 94%–100%[14]. Diagnosing disseminated disease is often difficult because patients are usually already severely ill with multisystem involvement and blood cultures turn out to be negative for growth. This diagnosis must be considered if there is evidence of infarction in multiple organs[26].

Reported independent risk predictors for development of invasive, disseminated zygomycosis are: Burns, premature neonate, deferoxamine use, diabetes and HIV infection[9]. Nevertheless, isolated cutaneous mucormycosis (without dissemination) has a favorable prognosis and a low mortality if aggressive surgical debridement is done promptly[26].

Suspected mucormycosis is an emergency and requires rapid action. In cutaneous involvement, tissue samples must be sent for analysis as follows[34]. (1) Direct microscopy with fluorescence (calcofluor white) and histopathology with special stains (like hematoxylin–eosin, periodic acid–Schiff or Grocott methenamine silver. To confirm the diagnosis, aseptate/pauci-septate, nonpigmented hyphae, 6–16 μm wide, ribbon like with irregular branching pattern must be demonstrated. In addition, surrounding tissues show evidence of angioinvasion, vessel occlusion, perineural invasion, coagulative necrosis, and polymorphonuclear infiltration. (2) Culture performed on routine media at 30 and 37°C. Cotton white or greyish black colonies. (3) Molecular identification and immunohistochemical staining with specific primary reagents.

CT scans of the chest, sinuses, cranium, abdomen or other parts involved must be performed. Halo and reverse halo signs and pleural effusion are noted in chest CT in cases with pulmonary involvement. On CT angiography, vascular occlusion sign defined as interrupted vessel at the border of a focal lesion may be seen. Given the limitations of imaging studies, diagnosing mucormycosis almost always requires histopathological evidence of fungal invasion of the tissues. In addition, serology for galactomannan and 1,3-β-D-glucan may be performed[34]. Identification to the genus and species level is strongly recommended for improved epidemiological understanding of mucormycosis and antifungal susceptibility testing[35,36]. Species identification requires the use of molecular techniques for DNA detection, which may also yield faster results as compared to culturing the organism. However, their clinical utility is currently limited by lack of technique standardization and clinical validation[37]. Large-scale clinical studies are needed to evaluate the role of molecular approaches as the primary diagnostic modality of mucormycosis[38].

Before the introduction of amphotericin B in the 1960s, reported overall mortality from the infection was as high as 85%. The introduction of amphotericin B administered systemically is the first line of treatment for the infection and has reduced mortality to 40%–60%. In combination with aggressive surgical therapy, this is seen to decrease to 30%. Overall, four factors are deemed critical for achieving cure in mucormycosis[26]; namely, early diagnosis, treating the underlying predisposing factors, antifungal therapy, and aggressive surgical debridement. The significance of delay in diagnosis of mucormycosis may be underscored by the fact that several autopsy series have reported that up to 50% of cases are diagnosed postmortem[39-41]. Small, localized lesions, diagnosed early can often be surgically excised before they spread to cause extensive disease or disseminate[42]; while delayed diagnosis has been shown to result in dramatically worse outcomes (83% *vs* 43% survival)[43]. Unfortunately, so far there are no serum or molecular tests to allow rapid diagnosis of the entity. Thus, the treating physician must maintain a high index of clinical suspicion and aggressively pursue diagnostic biopsy in suspected cases for improved outcomes.

Mucoraceous fungi are resistant to most antifungals and amphotericin B is the most active drug, against most isolates. Amphotericin B may be administered as amphotericin B deoxycholate, liposomal amphotericin B or amphoterecin B lipid complex. Other investigational/adjunctive therapies with variable efficacy include triazoles like, itraconazole, ketoconazole, posaconazole, isavuconazole, caspofungin, hyperbaric oxygen, iron chelation, cytokine therapy such as interferon-λ, and granulocyte colony-stimulating factor, which may enhance phagocytic activity against the pathogen [26]. A major obstacle for clinicians to choose among the current available antifungal agents in treating mucormycosis is the lack of available randomized clinical trials. The 2016 recommendations from the European Conference on Infections in Leukemia-6, as well as the ESCMID/ECMM guidelines, advocate the use of a lipid formulation of amphotericin B as first-line therapy for mucormycosis[44,45]. The currently suggested dose for liposomal amphotericin B is 5 mg/kg/day and as high as 10 mg/kg/day for infection of the central nervous system. However, the optimal doses for antifungal agents are still an issue of controversy. In case of renal failure, dose of amphotericin B may be reduced or alternate antifungals such as posaconazole and isavuconazole may be used. Also, in cases of severe disease, rapid progression, or poor general condition, they may be given in addition to amphotericin B[46]. Hyperbaric oxygen may have a role as an adjunct to standard therapy because higher oxygen pressure improves the ability of neutrophils to kill the organism[47] and has been shown to inhibit the germination of fungal spores *in vitro*[48], although there is a lack of prospective clinical trials to definitely establish its role in the treatment of mucormycosis.

Mucormycosis is usually rapidly progressive, and antifungal therapy alone is often inadequate to control the infection. Surgical debridement has an important role because, various species of mucor may or may not be susceptible to available antifungal agents and some species may even be resistant to amphotericin B. Moreover, the hallmark angioinvasion, thrombosis, and tissue necrosis in mucormycosis result in poor penetration of these agents. Thus, even *in vitro* susceptibility of the pathogen is not a guarantee of its *in vivo* efficacy. The killing the pathogen is not sufficient and urgent surgical debridement is thereby necessary to remove the infected and necrotic tissue and optimize cure rates[49].

Currently, mortality rates for mucormycosis vary from 40% to 80% based primarily on predisposing factors and site of involvement. This can rise to 96% for those with disseminated disease[9,50]. Much of the variability in outcome is due to the various forms of the disease. With respect to site of involvement, mortality is shown to be highest among patients with disseminated disease (68%) and lowest in those with cutaneous disease (31%)[16,23].

Independent risk factors associated with significantly increased mortality include disseminated disease, extensive burns, hematological malignancies, associated renal failure, delayed initiation of therapy and neonatal age group[9,16,34]. Conversely, lower mortality is seen in patients with immunocompetent status; without comorbidities; or with localized infection of the sinuses or skin and soft tissues, where early tissue-based diagnosis may be obtained and cure may be possible with early complete surgical debridement[34].

The case reported by us had delay in referral and administration of proper wound care. There could also have been contamination of dressings during 2 mo before reporting to the burn center. Although rapid diagnosis and surgical debridement were done when the patient finally reported to our center, the infection was already at the invasive stage. This further led to hematogenous dissemination with major vessel thrombosis, and pulmonary involvement.

CONCLUSION

Incidence of mucormycosis complicating burn wounds ranges from 0.1% to 0.6%, which may rise to 10%–15% during localized outbreaks in treatment units. The most common clinical form of mucormycosis in burn patients is cutaneous with higher propensity for dissemination than cutaneous involvement from other causes. Arterial invasion invariably occurs with embolization, thrombosis and infarction. Vascular invasion by the hyphae leads to progressive tissue necrosis. Despite improved understanding of the disease and the availability of more therapeutic options, survival rates in mucormycosis remain poor[9,16,26].

Maximizing survival rates requires rapid diagnostic and therapeutic intervention[34]. Patients with suspected mucormycosis should be referred immediately to a facility with the highest care level. The capability of diagnosing mucormycosis depends on the availability of mycological and histological investigation facilities and trained personnel. When diagnosed, early localized cutaneous mucormycosis treated with aggressive surgical debridement and adjunctive antifungal therapy. Care providers should be especially vigilant for wound infections in patients who demonstrate progressive necrosis outside of the area of initial burn wound. Wound surveillance seems to be the gold standard to avoid the devastating outcome of this rare, life-threatening infection. Treating surgeons must keep a high index of suspicion and send multiple wound biopsies when faced with a nonhealing burn raw area, especially in cases presenting late or with pre-existing immunocompromised state.

FOOTNOTES

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ORCID number: Atul Parashar 0000-0003-1617-6732; Chandra Singh 0000-0002-9971-3021.

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CASE REPORT

Community-acquired multidrug-resistant pneumonia, bacteraemia, and infective endocarditis: A case report

Basavaraj Jatteppanavar, Arnab Choudhury, Prasan Kumar Panda, Mukesh Bairwa

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Basavaraj Jatteppanavar, Arnab Choudhury, Prasan Kumar Panda, Mukesh Bairwa, Department of Medicine, All India Institute of Medical Sciences, Rishikesh 249203, India

Corresponding author: Prasan Kumar Panda, MBBS, MD, Associate Professor, Department of Medicine, All India Institute of Medical Sciences, Veer Bhadra Road, Rishikesh, Uttarkhand, 249203, India. motherprasanna@rediffmail.com

Abstract

BACKGROUND

The prevalence of multidrug-resistant (MDR) bacteria has increased globally, with extensive drug-resistant (XDR) bacteria posing a threat to patients.

CASE SUMMARY

This case report describes a young man admitted for suspected tropical fever infections who experienced rapid deterioration in health. Despite negative results for tropical fever infections, he had neutrophilic leucocytosis, acute kidney injury, and chest imaging findings suggestive of bilateral consolidations. On day two, he was diagnosed with infective endocarditis with possible rheumatic heart disease and MDR methicillin-resistant *Staphylococcus aureus* bacteraemia, and community-acquired pneumonia. Despite treatment with broad-spectrum antibiotics, he did not respond and succumbed to death on day five.

CONCLUSION

This case highlights that clinicians/public should be aware of MDR community-acquired pneumonia, bacteraemia, and endocarditis which ultimately culminate in high rates of morbidity and mortality. Early identification of pathogenic strain and prompt antibiotic treatment are a mainstay for the management and prevention of early fatalities. Simultaneously, route cause analysis of community-acquired MDR/XDR pathogens is a global need.

Key Words: Antibiotic resistance; Community-acquired infections; Infective endocarditis; Methicillin-resistant staphylococcus aureus; Rheumatic heart disease; Case report

Core Tip: A case of community-acquired multidrug-resistant methicillin-resistant *Staphylococcus aureus* infection leading to death is reported. The detection of CTX-M, VIM, NDM, mecA/C, and MREJ genes in microbial gene testing suggests that the patient was infected with MDR bacteria.

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INTRODUCTION

Antimicrobial drug resistance remains a global healthcare problem and poses a significant challenge to physicians worldwide, as the prevalence of multidrug-resistant (MDR), extensive drug-resistant (XDR), and pan-drug-resistant bacteria has increased in many tertiary care centres globally[1-3]. XDR bacteria are the current threats to patients. XDR bacteria are typically isolated in nosocomial settings. However, community acquisition of these infections is less prevalent but increasing day by day. Community-acquired pneumonia is a common clinical illness caused by bacteria and other pathogens. When it is associated with XDR bacteria, it is a matter of concern as there is a high risk of complications such as bacteraemia and infective endocarditis[4]. *Staphylococcus aureus* (*S. aureus*) is one of the leading causes of bacteraemia, both in the community and in the hospital setting, which can result in complicated or metastatic infections such as pneumonia, infective endocarditis, or sepsis with multi-organ dysfunction[5]. When compared with methicillin-sensitive *S. aureus*, MRSA is one of the leading causes of *S. aureus* bacteraemia and is associated with significant mortality and morbidity and poor clinical outcomes[6,7]. There is a limited amount of literature specifically addressing the combination of MDR community-acquired pneumonia (CAP), bacteraemia, and infective endocarditis.

The incidences of bacteraemia in CAP patients are 4% to 18% and one prediction model predicts bacteraemia in these patients with the help of variables like using recent antibiotic treatment, liver disease, and three vital signs (systolic blood pressure < 90 mmHg, temperature < 35 °C or ≥ 40 °C, and pulse ≥ 125/min) and three laboratory abnormalities (blood urea nitrogen ≥ 30 mg/dL, sodium < 130 mmol/L, and white blood cell count < 5000/mm^3 or > 20000/mm^3)[8]. This bacteraemia associated with pneumonia can lead to septicemia and other systemic complications like infective endocarditis, mostly due to delayed antibiotic administration[9]. This triad of pneumonia, bacteraemia, and infective endocarditis is uncommon, and community-acquired MDR organism causing the triad is even rarer. We herein report such a case to raise public health concerns.

CASE PRESENTATION

Chief complaints

Fever and abdominal pain for 3 d, and vomiting, swelling in the lower limbs, and itching and rashes all over the body for 1 d.

History of present illness

A young man in his 20s, previously healthy and with no substance abuse, suddenly felt ill. For the past 3 d, he had been experiencing an intermittent, documented, high-grade fever with associated chills that did not resolve despite taking medication. He also had abdominal pain for 3 d, initially as acute onset persistent nonprogressive dull aching pain in the right hypochondriac region, which later became diffuse without any aggravating or relieving factors. He experienced 3-4 episodes of non-bilious, non-blood-stained vomiting containing food particles. Additionally, he had bilateral symmetrical painless swelling in the lower limbs, without any decreased urine output, burning micturition, frothy urine, haematuria, or pyuria. He initially sought medical attention at a local hospital and took some medication, but approximately 30 min later, he developed skin itching and rashes all over his body, which was suspected to be a drug reaction. Further evaluation revealed deranged renal function, and he was subsequently referred to our centre.

History of past illness

Non-contributory.

Personal and family history

Non-significant.

Physical examination

Upon presentation, the patient was fully conscious of tachycardia and tachypnoea and maintained saturation at room air. A general physical examination did not reveal any major findings, except for bilateral pitting edema. Abdominal examination showed diffuse tenderness and guarding without any rigidity, distension, or palpable organomegaly. The

patient was intubated due to acute hypoxic respiratory failure and subsequently shifted to the intensive care unit. On day two of admission, he demonstrated high-grade fever, accompanied by subconjunctival dot haemorrhages, erythematous skin and non-blanching hemorrhagic petechiae, mucosal and skin erosions, splinter haemorrhages, Janeway lesions, and bilateral pitting pedal oedema with pan systolic murmur at the mitral area. It is possible that the murmur might have been missed due to subjective variations in the examiner's assessment on the first day of examination (Figure 1).

Laboratory examinations

The patient's initial laboratory tests showed an increase in neutrophilic white blood cells with a decrease in platelet count, along with an elevated level of procalcitonin at 38 ng/mL (normal range, < 0.05 ng/mL; a marker for bacterial infection) and acute kidney injury (Table 1). A peripheral blood smear revealed normocytic normochromic cells with toxic granules, indicating toxic changes in white blood cells. Further investigations revealed disseminated intravascular coagulation, as evidenced by elevated levels of prothrombin time/international normalized ratio, activated partial thromboplastin clotting time, and D-dimer. As per institution policy and surviving sepsis guidelines 2021, the patient had clinical and biochemical evidence of definitive sepsis. Hence, two sets of blood cultures were sent before administration of antibiotics. Workups for tropical fever infections such as corona virus disease 2019, H3N2 and H1N1 influenza virus infection, dengue, malaria, scrub typhus, leptospira, and typhoid were negative. Arterial blood gas analysis showed normal anion gap metabolic acidosis with lactic acidosis and acute hypoxic respiratory failure.

Blood cultures were sent for suspected infective endocarditis, and after 48 h of incubation, two sets of blood cultures revealed MDR methicillin-resistant *Staphylococcus aureus* (MRSA), which was sensitive to linezolid, vancomycin, clindamycin, and tigecycline, but resistant to penicillin, ciprofloxacin, levofloxacin, erythromycin, co-trimoxazole, and gentamicin. On the fourth day of admission, nested multiplex PCR (BioFire^{R}) test of an endotracheal aspirate revealed the presence of *Pseudomonas aeruginosa, Staphylococcus aureus*, human rhinovirus, and enterovirus but sterile on culture. Microbial gene testing detected the presence of mec A/C (MRSA) cassette, which confers resistance to methicillin and other beta-lactam antibiotics, and MREJ genes (Mobile RmtE/J group genes, which encode rRNA methyltransferases that confer resistance to aminoglycoside antibiotics). The urine culture was sterile.

Imaging examinations

Ultrasonography of the abdomen showed hepatosplenomegaly, and an X-ray of the abdomen did not reveal any acute surgical emergencies. Chest X-ray showed bilateral areas of opacity in the middle and lower lobes of the lungs with air bronchograms. High-resolution computed tomography (HRCT) of the thorax revealed consolidation and air bronchograms in bilateral lung areas, along with interspersed ground glass opacities and bilateral pleural effusions (Figure 2). A two-dimensional echocardiography was done due to high suspicion of infective endocarditis, which revealed findings suggestive of rheumatic heart disease: Moderate mitral regurgitation, moderate mitral stenosis, mild aortic regurgitation, thickened anterior mitral leaflet with hockey stick sign with restricted leaflet motion, dilated left atrium, vegetations on the mitral valve, and a left ventricular ejection fraction of 50%.

MULTIDISCIPLINARY EXPERT CONSULTATION

Based on the presentation and baseline investigation, two differential diagnoses were considered. The first was pulmonary-renal syndrome, characterized by diffuse alveolar haemorrhage and glomerulonephritis, which can be caused by any underlying autoimmune disorder. This often presents with new onset bleeding from the respiratory tract, respiratory distress with hypoxia, and bilateral confluent opacities seen on HRCT of the thorax. However, severe thrombocytopenia and bilateral effusion, which are not typical findings of vasculitis, did not support this diagnosis. Furthermore, these opacities could be explained by community-acquired pneumonia as the patient's endotracheal aspirate bio-fire test was positive for *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Antinuclear antibodies tested were negative by indirect immunofluorescence assay, so further serological workup for autoimmune conditions was not pursued.

The second differential diagnosis was severe fever with thrombocytopenia syndrome, an acute febrile illness characterized by fever, thrombocytopenia, leukopenia, and gastrointestinal symptoms. It is transmitted to humans by tick bites, primarily from *Haemaphysalis longicornis, Ixodes nipponensis, Rhipicephalus microplus,* and *Amblyomma testudinarium*. This syndrome is associated with a high fatality rate and can lead to multiple organ failure and death[8]. However, the patient tested negative for other endemic tick-borne diseases like scrub typhus.

FINAL DIAGNOSIS

The patient had community-acquired pneumonia associated with MRSA, bacteraemia, and infective endocarditis.

TREATMENT

The diagnosis of infective endocarditis was made according to the modified Dukes' criteria, in addition to community-acquired pneumonia, sepsis with multi-organ dysfunction syndrome, shock, encephalopathy, severe acute respiratory

Table 1 Result of basic investigations during hospitalization of the patient

Investigation	Normal range and unit	March 17, 2023	March 18, 2023	March 20, 2023	March 21, 2023	March 22, 2023
Hemoglobin	13-17 g/dL	14	14.2	11	10.2	10.2
Total leucocyte count	4-11 × 10^3/μL	12700	18740	36677	27232	27800
Neutrophil percentage	40%-70%	91	92.6	87.3	84.2	81
Lymphocyte percentage	20%-40%	5	3.2	7.4	13.4	14.2
Monocyte percentage	2%-8%	2	2.2	4.7	2.2	4.6
Eosinophil percentage	1%-6%	1	1.2	0.3	0	0
Basophil percentage	< 2%	0.2	0.8	0.3	0.2	0.2
Platelets	150-400 × 10^3/μL	69 × 10^3	45 × 10^3	20 × 10^3	57 × 10^3	57 × 10^3
Total bilirubin	0.3-1.2 mg/dL		5.9			3.96
Serum glutamic oxaloacetic transaminase	0-50 U/L		58			320
Serum glutamate pyruvate transaminase	0-50 U/L		50			1319
Alkaline phosphatase	30-120 U/L		195			191
Gamma-glutamyl transferase	0-55 U/L		62			99
Urea	17-43 mg/dL	64	223	216	289	
Creatinine	0.72-1.18 mg/dL	1.67	2.04	1.51	1.61	
Sodium	136-146 mmo/L		136	147	155	
Potassium	3.5-5.1 mmo/L		4.2	3.9	3.9	
Prothrombin time	12.3 s		14.7	13.7		20.5
International normalized ratio	1.14		1.37	1.27		1.94
Activated partial thromboplastin clotting time	22.1-28.1 s			29		26
Fibrinogen	180-350 mg/dL			398.6		265
D-dimer	0-0.5 mg/dL			> 5.5	> 5.5	> 5.5
Procalcitonin	0.5 ng/mL		38			
Antinuclear antibodies			Negative			

distress syndrome, acute kidney injury, and disseminated intravascular coagulation. Intravenous (IV) vancomycin 15 mg/kg every 12 h, gentamicin 1 mg/kg every 8 h, and meropenem 1 g every 8 h were started as empirical antibiotics. Ventilator settings were optimized according to the acute respiratory distress syndrome (ARDS) protocol, and sedation and neuromuscular blockade were administered. Prone positioning was also done. Dual vasopressor support was implemented to maintain a mean arterial pressure above 65 mmHg. Approximately 14 units of fresh frozen plasma and 10 units of random donor platelets were used to treat continuous endotracheal bleeding and Ryle's tube bleeding. Antipyretics were given to control fever spikes, and therapeutic hypothermia measures were also followed. After the culture reports, the injection of meropenem was stopped, and ceftazidime-avibactam and aztreonam were started in their place. Gentamicin was stopped, vancomycin was continued, and colistin was administered through nebulization. The patient rapidly progressed to septic shock and multiorgan dysfunction. Despite being on 100% FiO2, hypoxia and saturation levels worsened, leading to severe ARDS.

OUTCOME AND FOLLOW-UP

Despite aggressive treatment, the patient's bacteraemia did not respond and had a fulminant course, and the patient eventually succumbed to death on the fifth day of admission due to severe ARDS.

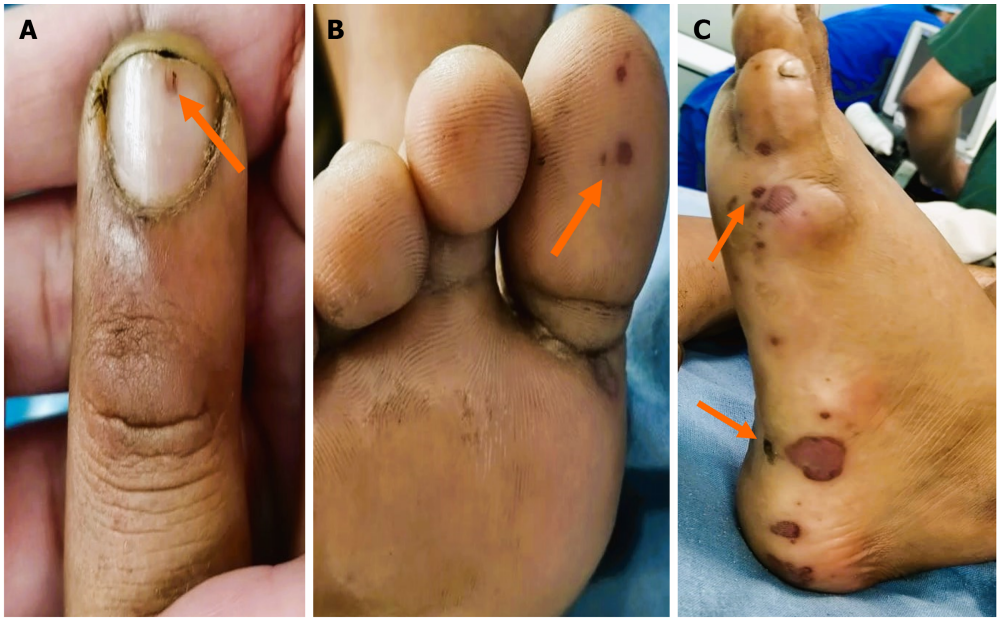

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Figure 1 Peripheral manifestations of infective endocarditis. A: Splinter haemorrhage (arrow) - a minute petechiae on the bed of a fingernail; B and C: Janeway lesions (arrows), multiple small haemorrhages with slight nodularity on the sole of the feet.

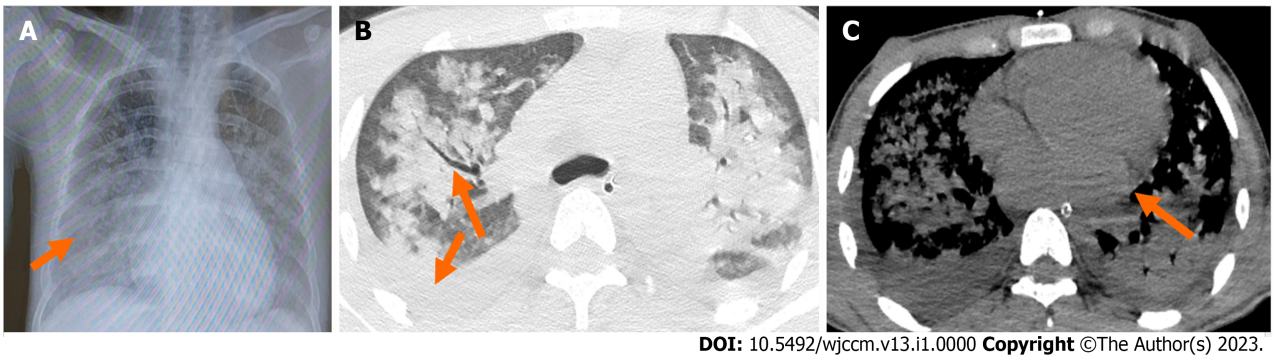

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Figure 2 Radiological images of the thorax. A: Frontal X-ray in a sitting position shows bilateral opacities (arrow); B: Computed tomography image through the middle and lower lobes show bilateral lung areas of consolidation and air bronchograms (arrow), along with interspersed areas of ground glass opacities and bilateral pleural effusions (arrow); C: Mediastinal window of the thorax showing cardiomegaly (arrow).

DISCUSSION

Community-acquired MDR (CA-MDR) infections are infections that are acquired outside of healthcare settings and are caused by microorganisms that are resistant to multiple types of antibiotics. CA-MDR infections are a significant public health concern, particularly in developing countries where inadequate healthcare facilities, poor sanitation, and limited access to antibiotics contribute to the spread of these infections. CA-MDR infections can be transmitted through direct contact with contaminated surfaces or through person-to-person contact, and risk factors include overuse and misuse of antibiotics, poor sanitation and hygiene, lack of access to clean water, crowded living conditions, poor infection control practices in healthcare settings, immunosuppression, chronic illnesses, and malnutrition.

India is one of the countries where CA-MDR infections are a significant public health concern. Several studies and reports have highlighted the high prevalence of CA-MDR infections in India, as well as the challenges in addressing this issue. Of particular concern is the emergence of community-acquired MRSA infections in patients with no apparent risk factors at the community level, as seen in our case[10]. Community acquisition of MRSA infection is associated with significant morbidity and mortality, similar to nosocomial MRSA infection. Person-to-person transmission of community-associated MRSA has been reported[11]. Numerous studies, systematic analyses, and meta-analyses conducted in India have revealed a progressive rise in the incidence of MRSA and changes in resistance patterns. A systematic review and meta-analysis found that the prevalence of MRSA in India was relatively high at 27%, with a higher proportion observed among men aged > 18 years[12]. However, all MRSA isolates in India were found to be sensitive to vancomycin and teicoplanin. Resistance to cotrimoxazole, erythromycin, gentamicin, and other penicillins and cephalosporins appeared to be common features of MRSA isolates in India, consistent with other Indian studies and our patient[13]. Another study

conducted in a tertiary care centre in southern India also revealed a high level of resistance among MRSA isolates, with linezolid, piperacillin/tazobactam, and tetracycline found to be effective agents against MRSA[14]. CA-MRSA (community-acquired methicillin-resistant *S. aureus*) isolates are now being increasingly reported from India. D'Souza *et al*[15] studied 412 confirmed cases of MRSA and found that 54% were true CA-MRSA possessing the SCCmec (staphylococcal chromosomal cassette mec) IV and SCCmec V genes. These were mainly isolated from skin and soft tissue infections. CA-MRSA isolates also showed variable resistance to ciprofloxacin, erythromycin, clindamycin, and tetracycline. Chatterjee *et al*[16] found that the overall prevalence of *S. aureus* nasal colonization was 52.3% and that of MRSA was 3.89% in the community.

Addressing the issue of CA-MDR infections in India requires collaboration between healthcare providers, policymakers, and the public to promote responsible antibiotic use, improve infection control practices, and ensure effective treatment of infectious diseases.

Global analysis of burden of bacterial anti-microbial resistance (AMR) in 2019 has shown that AMR caused an estimated 1.27 million deaths and was associated with an estimated 4.95 million deaths worldwide in 2019, with drug resistance in lower respiratory and bloodstream infections having the greatest impact. Among the 23 pathogens studied, drug resistance in six (*E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa*) alone led directly to 929000 deaths and was associated with 3.57 million deaths. Resistance to fluoroquinolones and beta-lactam antibiotics accounted for over 70% of deaths caused by AMR. The health impact of pathogens varied widely based on location, with high-income countries most affected by *S. aureus* and *E. coli*, while in Sub-Saharan Africa, *K. pneumoniae* and *S. pneumoniae* caused the most deaths. The study emphasized the need for improved global data collection to address the most pressing challenges posed by AMR[17].

Preventing CA-MDR infections requires a multifaceted approach that involves improving sanitation and hygiene practices, promoting responsible antibiotic use, improving infection control practices in community settings, and increasing access to healthcare for vulnerable populations. This includes educating the public about the importance of appropriate antibiotic use and supporting initiatives to reduce the overuse and misuse of antibiotics, as well as implementing effective infection control measures in community settings and providing access to affordable and quality healthcare for all individuals. Additionally, developing new antibiotics and alternative treatments, monitoring and tracking CA-MDR infections, and educating healthcare providers and the general public on CA-MDR and its risks are essential.

Overall, CA-MDR infections represent a significant public health concern, and addressing this issue requires collaboration between healthcare providers, policymakers, and the public to promote responsible antibiotic use, improve infection control practices, and ensure effective treatment of infectious diseases.

CONCLUSION

There is a growing threat of MDR bacteria in the community setting in patients with no apparent risk factors. The presence of a CA-MDR MRSA strain increases the risk of treatment failure and further spread of infection and associated complications. Better surveillance, infection control measures, and antibiotic stewardship programs are urgently needed in the community.

FOOTNOTES

Author contributions: Jatteppanavar B and Choudhury A contributed equally to this work; Jatteppanavar B, Choudhury A, Bairwa M, and Panda PK designed the research study, performed the research, and critically reviewed the manuscript; Jatteppanavar B and Choudhury A analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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ORCID number: Basavaraj Jatteppanavar 0000-0002-4792-4919; Arnab Choudhury 0000-0001-5947-572X; Prasan Kumar Panda 0000-0002-3008-7245; Mukesh Bairwa 0000-0002-8974-5775.

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