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Clinical management, education and research: a new must for modern intensive care physician!

The *Key Leaders' Opinion on Critical Care Medicine* (*AME Medical Review Series 003*), with Drs. Zhongheng Zhang (Jinhua municipal central hospital), Dr. jordi Rello (Vall d'Hebron University Hospital) and Ming Zhong (Zhongshan Hospital) as Editors of the book, focuses on mechanical ventilation, sepsis and infection, cardiac arrest and cardiopulmonary resuscitation, extracorporeal support, delirium and sedation, outcome of the critically ill patient, and methodology of study design.

Clinical management, education and training as well as research must be considered for optimizing the overall treatment of critically ill patients. These topics are of particular relevance not only in providing updated information but also to support clinicians in developing educational and training strategies as well as better interpretation and design of experimental and clinical studies.

The first section of the book is about mechanical ventilation. The most challenging pulmonary disease in critically ill patients is Acute Respiratory Distress Syndrome (ARDS), and its definition is relevant to improve individualization of treatment and future study design. Mechanical ventilation plays a relevant role in patients not only admitted to Intensive Care Unit, but also in the surgical and medical wards as well as out-of- the hospital. Non-invasive respiratory assistance is more commonly used but recent data provided new information about appropriate selection of patients and new available techniques. Protective mechanical ventilation has been proposed initially to improve outcome in patients with ARDS. However, recent large observational and randomized clinical trials showed that protective mechanical ventilation with low tidal volume and inspiratory pressures is also useful to reduce complications and improve survival in patients without ARDS, even those undergoing high risk surgery. The second section is focusing on sepsis and infection. New definition of sepsis has been recently proposed and largely discussed in the present book. Most importantly, it has been developed the concept that prevention is better than cure, when possible. In other words, early monitoring of sepsis may provide adequate treatment and clinical management avoiding possible severe complications, associated with poor survival. Further, the diagnosis and management of sepsis and septic shock includes the control of fever, optimization of antibiotic treatment, prevention of catheter related infections, hospital acquired pneumonia, as well as new monitoring techniques like those on microcirculation monitoring. The optimal hemodynamic management with a rationale choice for fluid management is also discussed in this part of the book. The third section is dedicated to cardiac arrest and cardiopulmonary resuscitation, focusing on optimization of chest compressions, as well as target temperature management. Delirium and sedation as well as outcome of critically ill patients are discussed in the fourth and fifth section. It has been recently pointed out that the goal of intensive care is not only to provide assistance in the acute phase of the disease but also to result in an acceptable good quality of life after discharge of the hospital and at home, avoiding the occurrence of so called "disabled patient". This discussion has also relevant ethical consequences, with differences between countries to countries. Control of delirium, as well as pain and agitation, which are specifically discussed, play a major role to improve outcome and quality of life of critically ill patients. The sixth section is dedicated to extracorporeal support, which is more commonly used not only in cardiac intensive care but also for providing organ support in patients with respiratory or renal failure. Finally, the seventh section is about the methodology of study design. Scientific medical literature is dramatically growing in these last years. This is markedly important from an educational point of view since it is now recommended that research and correct interpretation and discussion of papers published become part of the education and training of the modern intensive care physician.

In conclusion, this book provides new updated information about debate on clinical management of critically ill patients, which is becoming interdisciplinary, and requiring specific knowledge in different areas of medicine and surgery.

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The critical care medicine is in a continuous research for better care to patients admitted to ICU with failing key organ function in a very broad medical setting. By definition, patients admitted to ICU have used all their intrinsic resources and adaptive mechanisms are overwhelmed facing an acute illness. The patients we are to admit to our units are almost at the point to lose the battle. That means that we have to quickly assess the clinical scenario and deliver the most adequate and efficient support to the failing response of the body. The knowledge in this area of medicine is expanding dramatically, making concepts and recommendations the intensivists have to keep up more and more complex and continuously evolving. Therefore, point-of-knowledge updating the number of new results and findings that regularly feed the literature each year is welcome. This is the purpose of this book.

This book entitled "*Key Leaders' Opinion on Critical Care Medicine*" provides indeed a very interesting compilation of 44 review or editorial papers written by experts in the field of intensive care medicine. They had basically worked on original papers, which, for most of them, were published in the last year in top ranked journals. Organized in different sections, the two largest parts of the articles are dedicated to both mechanical ventilation and acute respiratory distress syndrome one hand and sepsis on the other hand. These areas are really the core of our daily practice.

The authors reanalyzed the articles in details and produced thorough comments about methods and data used in the original studies. Therefore, throughout this book are displayed three among the basic tenets upon which the clinical research in the ICU is founded, namely epidemiology, pathophysiology and clinical trials. Furthermore, the selected original papers were put in some perspective: which gaps had bridged the study, what should be done in the future from the new findings. Several articles were used for a given topic. As an example, three articles deal with noninvasive ventilation in immunocompromised patients with acute respiratory failure, three others with the management of fever in the ICU, four papers with delirium and sedation assessment and management and three with catheter-related infections in the critically ill. Moreover, different experts gave specific comments for a given topic and that enhanced and enriched the appraisal of the original studies.

Finally, two papers explored two ways for handling and designing future studies. In one paper, a method was proposed to take into account some imbalance between groups at the time of randomization in trials and to quantify the weight this imbalance may have in the effect size of the tested intervention or strategy. Another paper dealt with the issue of the selection of patients to be included in trials in the current era of personalized medicine. Instead of including a large population of patients, the authors proposed to select patients upon their physiologic response to a given intervention, for instance the oxygenation response to positive end-expiratory pressure, and to test the intervention versus a control in those who responded positively.

This book is very stimulating and I hope you will enjoy reading it as much as I have had in going through.

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The book *Key Leader's Opinion on Critical Care Medicine* is a member of a series of AME commentary books. This is a great adventure to explore a new style of publication. All authors invited to contribute to the book are key leaders in their specialties or subspecialties. Their insightful comments on a particular issue are worthwhile in that it not only helps to incorporate new evidence into clinical practice but also directs future researches. Most of the comments are made on original articles published in prestigious peer-reviewed journals such as *The Lancet*, *The New England Journal of Medicine*, *Intensive care medicine and Critical Care medicine*. Although not exhaustive, articles published in these journals cover the most important researches and reflect the state-of-the-art understanding on critical care medicine. However, one original research can lead to different interpretations and there will be disparities in subsequent changes of clinical practice. As a result, presenting the result of large clinical researches to clinicians is not the end of the story. Interpretations of the results and how to incorporate the results into clinical practice are also interesting and important. As the motto goes: there are a thousand Hamlets in a thousand people's eyes. We found that different authors can have different views and points on a research, and all of them are valuable. For junior clinicians, these insightful thoughts help to sharpen their ideas to form the directions of future research.

At the beginning of the year 2015, AME publishing company launched this project and the subject covers all areas of clinical medicine. We found that our book is numbered 003, suggesting other section editors are much more hard-working than us. I'm honored to work with them. The publication style is unique in that these comments are firstly published in AME journals and then they are compiled into a book. Publication in journals ensures the timeliness of the dissemination of these opinions. Usually, an important work can stir great debate in the specialty community. For instance, when several major trials on the effectiveness of early goal directed therpy (EGDT) were published in 2005, many journals published commentary papers immediately. This reflects the requirement of timeliness for commentary. While journal articles ensure timeliness, compiling them into a book means that these views and perspectives are immortal and have far-reaching impact (e.g., they will not disappear as time goes by). It will be exciting if some thoughts shaped in these commentaries will be validated and find its way into daily clinical practice. There is an interesting column in the journal *Intensive Care Medicine*, which is called "my paper 20 years later". They invited authors to comment on their research published decades ago. Maybe in the future, we can also invite authors to comment on the views that have been made years before, by incorporating new evidence at that time.

Lastly, I would like to thank AME publishing company to give us such a platform to exchange ideas and views. Also, I would like to thank my family. Without their support, my dreams will not come true.

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The editorial process is based on submission of originals to reviewers, which are assessed by blinded pairs, with the aim to improve the final manuscript. At the end of the process, when published, the manuscript has gained consistency and the take home message is better. This is important because authors look for maximal visibility.

Interpretation of findings, weaknesses and strengths are part of the discussion section of a manuscript. However, most manuscripts may have a different perspective, with implications on future practice and research. Therefore, an expert comment by an opinion leader is often giving a different perspective. Indeed, we learned a lot looking at different interpretations of our own articles in scientific meetings or in accompanying comments.

This book is a compilation of comments done by expert opinion leaders of articles recently published in critical care. It covers a broad spectrum of topics, with special emphasis on mechanical ventilation, sepsis and sedation. It provides an update of first line research on their respective topics.

It provides also valuable information for the practitioner, who has limited time to review the vast scientific production and to non specialist that need to focus a specific article in a perspective. Moreover, fellows have a great opportunity to learn to read between lines if they compare original articles with expert reviews by opinion leaders.

Hippocrates mentioned that "*it is more important to know what sort of a person has a disease than what sort of disease a person has*". This book responds to this statement and proves that personalized medicine is the great challenge that we have now in critical care.

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Over the past four decades, critical care medicine has become increasingly complex. Hence, critical care medicine is a cutting-edge medical field that is highly evidence-based. Studies are continuously published that alter the approach to patient care. There is an old Chinese saying "Both sides must present their opinions." (兼听则明，偏听则暗). Even the most well-designed studies could not solve everything.

As one of the "*Key Leaders' Opinion*" series produced by AME, the book contains the commentaries written by 40 key leads with outstanding academic reputation on most recent influential studies in the field of critical care medicine. The articles in this book cover a wide range of topics that are relevant to sepsis, infection, mechanical ventilation, extracorporeal life support, nutrition, etc. It's editors' hope that this book will provide clinicians practicing in the intensive care unit with a reference to understand those extraordinary studies and to help guide their care of critically ill patients.

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Supporting respiratory function in the immunocompromised critically ill patient: new perspectives for an old paradigm

Lorenzo Ball, Paolo Pelosi

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Delivering care to patients suffering from a severe depression of the immune system is a challenge for the intensivist. Such patients pose relevant issues in terms of choice of the appropriate treatment and resource allocation, as well as relevant ethical issues in both clinical practice and research. Especially in the past, the poor prognosis improvement achieved with intensive treatment among these patients lead critical care givers to be reluctant in admitting them to the intensive care unit (ICU) for two main reasons: the willingness to avoid relentless treatment and the perception of ICU as a high-risk setting for contracting multiresistant microorganisms (1). Acute respiratory failure (ARF) is a common complication in these patients, and the leading reason requiring admission to the ICU (1-3). For many caregivers the idea that immunocompromised patients are unlikely to benefit from ICU admission has been a paradigm for long time.

The last decade was characterised by several changes in epidemiology, prognosis and treatment of immunocompromised patients admitted to the ICU. First, the proportion of individuals in the general population living with different degrees of suppression of the immune response due to haematological malignancies, solid tumour, chemotherapy and immunosuppressive treatments for chronic non-oncological conditions is steadily increasing (4). Second, the observed outcome after unplanned admission to the ICU of oncologic patients is higher that of non-immunocompromised ones, but is better that that observed in previous studies (1,3,5). As a result, the admission to the ICU of this subpopulation of patients is increasing (3), and the attitude of intensivists is slowly changing accordingly (6). In a recent observational study in Netherlands, the proportion of haematological patients admission increased by 6% per year from 2004 to 2012 (3), and this is likely to reflect the tendency of many other high-income countries. In another retrospective study, immunocompromised patients were not found to be more prone than matched controls to be develop infections by multidrug resistant bacterial strains during the ICU stay (7).

It is matter of intense debate whether the higher survival rates are due to specific changes in care delivery (8), or merely reflect the general improvement of ICU mortality (9).

Intubation and invasive mechanical ventilation was earlier identified as an independent predictor of mortality among immunocompromised patients, and this provided the rationale for few small-sampled randomized trials investigating the role of non-invasive positive pressure ventilation (NPPV) as a tool to avoid intubation, thus potentially improving outcome (10,11). The encouraging findings of these trials lead to a widespread acceptation of NPPV as a first-choice tool for early treatment of ARF among haematological and oncological patients (12).

In a randomized trial recently published on *JAMA* by the French-Belgian network "*Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique*", Lemiale and colleagues compared early intermittent NPPV to oxygen therapy in immunocompromised patients, hypothesizing that the former could reduce mortality at 28 days in patients developing ARF (13). This study was rigorously conducted,

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and its protocol was registered and published before the end of patients enrolment (14). The authors screened for inclusion 680 subjects in the 28 participating hospitals, randomizing a total of 374 patients with a 1:1 ratio. In the intention-to-treat analysis testing the superiority hypothesis, the trial found no differences between NPPV and oxygen therapy in any of the pre-defined primary and secondary outcomes, including all cause 28-days mortality, need and duration of invasive mechanical ventilation, changes in sequential organ failure assessment (SOFA) score, ICU-acquired infections, length of ICU and hospital stay as well as mortality and performance status at 6 months. It is opinion of the authors of the present editorial that several peculiarity of this study makes the interpretation and generalization of the results particularly complex.

Immune system deficiency was defined as the presence of haematological or solid malignancies, regardless of the timing of last chemotherapy course, or long term high dose immunosuppressive therapy. Patients with a recent onset of hypoxemic ARF were screened for inclusion, excluding those with hypercapnia, heart failure, need for high dose vasopressors, or other contraindications for NPPV. The study found no differences between immunodeficiency due to haemato-oncological conditions and immunosuppressive treatment. Differences between solid tumours and haematological disease were not investigated, but predicted mortality should have been similar according to a previous observational study (3). Half of the patients in both arms had received chemotherapy shortly prior to ICU admission, but it was not planned to analyse whether this subgroup had a higher mortality.

As observed by the authors themselves, this study's power was lower than expected. A priori sample size calculation was rigorously based on previous studies: a 28-days mortality as high as 35% was expected in the control arm, but observed mortality in both arms was significantly lower (27% and 24%). Most of the outcomes show a slight trend favouring NPPV: this might suggest that further studies are warranted before concluding that NPPV should be abandoned in these patients. Moreover, caregivers were given the option to choose humidified high flow nasal cannulas (HHFNC) as an alternative to conventional oxygen delivery in the control arm, and in the intervention group between NPPV courses. This could have contributed to the unexpectedly low mortality in the control arm. A recent large randomized trial study found that HHFNC in ARF can halve 90-days mortality in the general population compared to both standard oxygen and NPPV, with an unclear mechanism apparently not mediated by the reduction of the intubation rate, that was found to be comparable (15). Lemiale *et al.* also conducted a separate pilot study investigating HHFNC in immunocompromised patients with negative results (16), but the outcome was the need for respiratory assistance in a short time window. Therefore, we agree with the authors that further studies comparing conventional oxygen, NPPV and HHFNC are needed to provide the clinicians with a definitive answer on how to manage ARF in the immunocompromised patient. However, this need raises some ethical problem. As often occurs in evaluating rescue therapies, for patients enrolled in the control arm of randomized trials that have mortality as primary endpoint, it is hard to deny the access to treatments whose efficacy is proven or at least alleged. Lemiale and co-workers seem to have considered these aspects, and found a fair and reasonable compromise between scientific robustness and quality of care. Nonetheless, this could have played a role in reducing the achieved statistical power. This issue has to be addressed carefully in the design of future trials in the field.

Concerning the type of intervention, all the randomized trials published so far have investigated the efficacy of early intermittent NPPV: short cycles of around one hour were alternated with few hours of spontaneous breathing under oxygen therapy, immediately after the onset of specific criteria defining ARF (10,11,13). Other indications, timing and course duration could affect the clinical outcome, therefore they could be considered for investigation.

NPPV is a valid option when respiratory failure occurs because of a reversible underlying cause, and when it does not represent only a delay to an unavoidable intubation (17). Among immunocompromised patients it is particularly difficult to predict NPPV efficacy identifying patients who can benefit from its application. Efforts should be made to identify specific subgroups of patients in which NPPV can effectively modify the course of the respiratory failure.

Despite the solidity of this new randomized controlled trial, we do not believe that the available evidence should be interpreted as a definitive indication to discontinue the recourse to NPPV to relief ARF in immunocompromised patients. Rather, the clinicians should be aware that short courses of NPPV alone does not seem to provide benefits that surpass those that can be achieved by oxygen therapy, including HHFNC. This does not exclude that in specific cases NPPV could improve outcome.

At the moment further studies are necessary to provide an answer on how one should treat ARF in an

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immunocompromised patients: pending more definitive data, a meticulous clinical judgement that takes into account the conflicting results of the most recent studies should be the guidance to the management of these conditions.

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Footnote

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New puzzles for the use of non-invasive ventilation for immunosuppressed patients

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Abstract: On October 27, 2015, Lemile and colleagues published an article in *JAMA* entitled "Effect of Noninvasive Ventilation *vs.* Oxygen Therapy on Mortality among Immunocompromised Patients with Acute Respiratory Failure: A Randomized Clinical Trial", which investigated the effects of non-invasive ventilation (NIV) in 28-day mortality of 374 critically ill immunosuppressed patients. The authors found that among immunosuppressed patients admitted to the intensive care unit (ICU) with hypoxemic acute respiratory failure, early NIV compared with oxygen therapy alone did not reduce 28-day mortality. Furthermore, different from the previous publications, there were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays. The study power was limited, median oxygen flow used was higher than used before or 9 L/min, NIV settings provided tidal volumes higher than what is considered protective nowadays or from 7 to 10 mL/kg of ideal body weight and the hypoxemic respiratory failure was moderate to severe (median PaO_2/FIO_2 was around 140), a group prone to failure in noninvasive ventilatory support. Doubts arose regarding the early use of NIV in immunosuppressed critically ill patients with non-hypercapnic hypoxemic respiratory failure that need to be solved in the near future.

Keywords: Non-invasive ventilation (NIV); acute respiratory failure; immunosuppression

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In a landmark trial published in 2001, Hilbert and colleagues (1) showed that in selected patients with immunosuppression, pulmonary infiltrates, fever, and hypoxemic acute respiratory failure, early implementation of non-invasive ventilation (NIV)—was associated with a significant reduction in the rate of endotracheal intubation, serious complications, death in the intensive care unit (ICU), and death in the hospital. Indeed, avoiding intubation should be an important objective in the management of respiratory failure in immunosuppressed patients since it impedes the risk of severe complications such as ventilator associated pneumonia (VAP), barotrauma and ventilator-induced lung injury (2,3).

Subsequently, Antonelli and colleagues (4) showed that the use of NIV in patients undergoing solid organ transplantation with acute hypoxemic respiratory failure compared to oxygen alone decreased the need of endotracheal intubation, the rate of fatal complications, length of ICU stay, ICU mortality but not hospital mortality. Based on these results, a clinical practice guideline suggested that NIV should be used for immunosuppressed patients who have acute respiratory failure, with a grade 2B recommendation (5). Members of this panel, however, questioned the generalizability of the results from centers with highly experienced staff to other centers and this recommendation was debated and remained questioned (6).

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The major points of debate was that the mortality of immunocompromised patients has improved considerably since the publication of these two trials (7,8), and evidence showing that failure of NIV followed by delayed intubation may increase mortality (9).

Acute respiratory failures, together with shock are the main reasons for ICU admission in immunosuppressed patients (8). The long-term mortality of this group of patients is high and the presence of acute respiratory failure is independently associated with worse outcomes. The use of mechanical ventilation is associated with a mortality rate of 60%, imposing the need of alternative therapies for patients with acute respiratory failure (8). Based on this, several experts suggest that in immunosuppressed patients, acute respiratory failure should probably be managed initially with NIV (9,10).

The study of Lemiale and colleagues (11) analyzed the relationship between early use of NIV and 28-day mortality in a randomized controlled trial in 374 critically ill immunosuppressed patients. The authors observed that among immunosuppressed patients admitted to the ICU with hypoxemic acute respiratory failure, early NIV compared with oxygen therapy alone did not reduce 28-day mortality. Moreover, there were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays. In the cohort analyzed, bacterial pneumonia and *Pneumocystis jirovecii* pneumonia account for more than 50% of the causes of acute respiratory failure. As expected, the mortality rate in the Lemiale and colleagues study (11) was much lower than those of the previous randomized controlled trials (26.5% *vs.* 65.4% *vs.* 45.0%) (2,4). An important finding of Lemiale and colleagues study (11) was that among intubated patients, mortality was similar with the use or not of NIV or according to time from start of NIV and intubation confirming the importance of prompt start of invasive mechanical ventilation in patients failing the use of NIV. Also, opposite to what was suggested by previous studies, the use of NIV was not associated with decreased need of intubation and mechanical ventilation.

The overall mortality in the immunosuppressed critically ill population has declined in recent years due to advances in targeted chemotherapy, prophylactic use of antibiotics, and improved supportive care (12). In their study, Lemiale and colleagues (11) anticipated a higher baseline mortality of 35% in the Oxygen alone group to 20% in the NIV group. The lower than expected mortality with oxygen alone limited the power of their study to detect a significant between-group difference in mortality.

Recently, Frat and colleagues (13) showed that in patients with non-hypercapnic acute hypoxemic respiratory failure, treatment with high-flow nasal cannula (HFNC) was associated with a lower 90-day mortality compared to standard oxygen therapy, or NIV. In the Lemiale and colleagues trial (11), a greater proportion of patients in the oxygen alone group received a higher than usual oxygen through the nasal cannula and perhaps because of this median flow of 9 L/min, the benefits of NIV was diluted. Few studies assessed the impact of HFNC in immunosuppressed patients. Recently, Lemiale and colleagues reported that a 2-hour trial with HFNC improved neither mechanical ventilatory assistance nor patient comfort compared with oxygen delivered via a Venturi mask in immunosuppressed patients with hypoxemic acute respiratory failure (14). Indeed, as with NIV, failure of HFNC might cause delayed intubation and worse clinical outcomes in patients with respiratory failure (15).

As stated above, the delayed intubation in critically ill patients is associated with worse outcomes (16). In immunosuppressed patients, mortality was highest in patients needing intubation and invasive mechanical ventilation, particularly when started after the first three days in the ICU (12), thus, patients should be intubated as soon as necessary. Respiratory disease severity and hemodynamic failure at ICU admission were risk factors for invasive mechanical ventilation in subjects with malignancies admitted for acute respiratory failure, and patients with these risk factors should be considered for invasive mechanical ventilation (17).

A big observational study by Lemiale and colleagues (18) confirmed that in hematologic patients with acute respiratory failure, initial treatment with NIV did not improve survival compared to oxygen only. Wermke and colleagues (19) also showed that early NIV performed in the wards is ineffective in hypoxemic hematologic patients with acute respiratory failure. Finally, several experts suggest that NIV should be used with caution in this group of patients (6).

Another important point not addressed in the study by Lemaile and colleagues was the ventilatory parameters used in the patients undergoing NIV. The authors described in the Methods section of their study that "the pressure support level was adjusted to obtain an expired tidal volume of 7 to 10 mL/kg of ideal body weight". Several animal and clinical studies demonstrated that ventilation with high tidal volumes could induce VILI (3,20-22). Thus, the use of higher tidal volumes during NIV in the study by Lemiale and colleagues (11) could be associated with higher degrees

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of lung injury and worse outcomes, as suggested in a recent trial comparing HFNC to NIV and oxygen (12,23).

In conclusion, new puzzles were introduced in the evaluation of NIV use in immunosuppressed patients with acute hypoxemic respiratory failure: the innovative use of high flow oxygen via nasal cannula therapy , the use of NIV with non-protective or protective ventilation and algorithms to better evaluate the failure of both therapies leading to prompt early intubation and invasive protective mechanical ventilation. Further research, preferentially by means of a new multicentric randomized controlled trial, is needed to delineate the role of NIV versus other strategies of initial respiratory support in hypoxemic ARF in immunosuppressed patients. Severity and type of immunosuppression , type and severity of acute hypoxemic respiratory failure, number of organ failures, time between onset of acute respiratory failure and ICU admission, clear indications and contra-indications for NIV and or high flow oxygen therapy , type of interface and equipment use, strict NIV and high flow oxygen use protocol, early recognition of NIV or high flow oxygen failure , clear indications of intubation and invasive protective mechanical ventilation should be part of the prospective randomized protocol to answer the important clinical question if early NIV or high flow oxygen use will really improve outcome in immunosuppressed critically ill patients with acute hypoxemic respiratory failure.

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Footnote

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Non-invasive ventilation in immunocompromised patients with acute hypoxemic respiratory failure

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Abstract: The survival rate of immunocompromised patients has improved over the past decades in light of remarkable progress in diagnostic and therapeutic options. Simultaneously, there has been an increase in the number of immunocompromised patients with life threatening complications requiring intensive care unit (ICU) treatment. ICU admission is necessary in up to 15% of patients with acute leukemia and 20% of bone marrow transplantation recipients, and the main reason for ICU referral in this patient population is acute hypoxemic respiratory failure, which is associated with a high mortality rate, particularly in patients requiring endotracheal intubation. The application of non-invasive ventilation (NIV), and thus the avoidance of endotracheal intubation and invasive mechanical ventilation with its side effects, appears therefore of great importance in this patient population. Early trials supported the benefits of NIV in these settings, and the 2011 Canadian guidelines for the use of NIV in critical care settings suggest the use of NIV in immune-compromised patients with a grade 2B recommendation. However, the very encouraging results from initial seminal trials were not confirmed in subsequent observational and randomized clinical studies, questioning the beneficial effect of NIV in immune-compromised patients. Based on these observations, a French group led by Azoulay decided to assess whether early intermittent respiratory support with NIV had a role in reducing the mortality rate of immune-compromised patients with non-hypercapnic hypoxemic respiratory failure developed in less than 72 h, and hence conducted a multicenter randomized controlled trial (RCT) in experienced ICUs in France. This perspective reviews the findings from their RCT in the context of the current critical care landscape, and in light of recent results from other trials focused on the early management of acute hypoxemic respiratory failure.

Keywords: Non-invasive ventilation (NIV); respiratory failure; immunosuppression

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Introduction

The survival rate of immunocompromised patients, such as those with hematological malignancies, solid organ transplant, acquired immunodeficiency syndrome, and those receiving corticosteroid or cytotoxic therapy for a non-malignant disease, has progressively improved due to the remarkable advances in diagnostic and therapeutic options (1). Simultaneously, there has been an increase in the number of immunocompromised patients with life threatening complications (2-4), with recent studies showing that 15% of patients with acute leukemia and 20% of bone marrow transplantation recipients require intensive care unit (ICU) admission (5). The main reason for ICU admission in these patient populations is acute hypoxemic respiratory failure (5,6), which is associated with a high mortality rate, particularly when invasive mechanical ventilation is required (2,7). This raises the interest on

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non-invasive ventilation (NIV), a technique that provides ventilator assistance without the use of endotracheal tube. NIV carries the advantages of lower ventilator-associated pneumonia and sedation requirements when compared to invasive mechanical ventilation. Furthermore, although side effects of NIV have been described, including facial skin lesions, gastric distension and patient discomfort related to noise, claustrophobia, nasal or oral dryness and nasal congestion, their incidence is low and largely preventable with proper management of the technique (8). Therefore, applying NIV, and thus avoiding endotracheal intubation and invasive mechanical ventilation with its side effects (9,10), may potentially decrease the mortality rate in immunocompromised patients (5,11-13).

This perspective reviews the findings from a recent randomized controlled trial (RCT) assessing whether early intermittent respiratory support with NIV has a role in reducing the mortality rate of immunocompromised patients with non-hypercapnic hypoxemic respiratory failure in the context of the current critical care landscape, and in light of recent results from other trials focused on the early management of acute hypoxemic respiratory failure.

Current evidence and recommendations

Several small single center RCTs have demonstrated positive patient outcomes with the early use of NIV.

Hilbert *et al.* investigated this hypothesis in a seminal study published in 2001 (12). In this single center RCT, 52 immunocompromised patients (with immunosuppression from several different etiologies) were enrolled if they had pulmonary infiltrates, fever, and hypoxemic acute respiratory failure, defined by the presence of dyspnea at rest, respiratory rate greater than 30 breaths per minute and a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) of less than 200 mmHg while breathing oxygen. These patients were randomly allocated to receive either standard oxygen treatment via facemask or intermittent NIV. Compared to standard oxygen therapy, the group treated with NIV had lower rates of endotracheal intubation (12/26 *vs.* 20/26 patients, P=0.03), and in-hospital mortality (50% *vs.* 81%, P=0.02).

Antonelli *et al.* reported the efficacy of NIV in reducing the need of endotracheal intubation and invasive mechanical ventilation in immunocompromised patients after solid organ transplantation with hypoxemic respiratory failure (14). In approximately 2 years, 40 patients with a PaO_2:FiO_2 of less than 200 mmHg while breathing oxygen and active use of accessory respiratory muscles were randomized to receive either NIV or treatment with supplemental oxygen via Venturi Mask. The group treated with NIV demonstrated significantly lower rates of endotracheal intubation (20% *vs.* 70%, P=0.002) and ICU mortality (20% *vs.* 50%, P=0.05). However, no significant difference was found in the in-hospital mortality rate.

Moreover, a more recent RCT investigated the potential role of early use of continuous positive airway pressure (CPAP) in patients with hematological malignancies (15). Forty patients on the ward with bilateral infiltrates, respiratory rate greater than 25 breaths/min and an oxygen saturation of less than 90% while breathing on room air, were randomized to receive oxygen (FiO_2 =50%) either by facemask or helmet CPAP at 10 cmH_2O. Overall, significantly fewer patients treated with CPAP required NIV or invasive mechanical ventilation (4 *vs.* 16 patients; P=0.0002).

Based on these data, NIV is currently considered in many centers as first line treatment for hypoxemic respiratory failure in patients with various causes of immunosuppression (16). Moreover, the 2011 Canadian guidelines for the use of NIV in critical care settings suggested the use of NIV in immunocompromised patients with a Grade 2B recommendation (17).

However, these very encouraging results have not been confirmed in subsequent observational (18) and randomized clinical (19) studies. In particular, a recent randomized trial investigated the role of early application of NIV in 86 patients with hypoxemic respiratory failure after allogeneic hematopoietic stem cell transplantation (19). In this study, early treatment with NIV did not affect the rate of endotracheal intubation, ICU admission, or patient survival. However, these results may be significantly affected by the high crossover rate given that 16 out of 44 patients in the group allocated to the treatment with conventional oxygen alone received NIV for failure to achieve the oxygenation target.

Therefore, the beneficial effect of NIV in immunocompromised patients has recently been questioned (20). Most of the studies showing a beneficial effect of NIV did not stratify patients for the cause of immunosuppression or timing (early *vs.* late) of NIV application. Moreover, the expected mortality rate of immunocompromised patients with acute respiratory failure, although still high, has progressively decreased from 50–80% in the year 2001 (12) to current 20–60% (21-23). This is likely due to the advancement in the management

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of critically ill patients, with particular regards to invasive mechanical ventilation, with a consequent potential lower clinical impact provided by treatment with NIV (24).

These observations directed the French group led by Lemiale and Azoulay to a new equipoise on the efficacy of NIV in immunocompromised patients with acute hypoxemic non hypercapnic respiratory failure.

The new trial: can early non-invasive ventilation (NIV) reduce mortality in immunocompromised patients with acute hypoxemic respiratory failure?

A multicenter RCT was conducted (25) to assess the potential benefit of early NIV in reducing the mortality rate among immunocompromised patients who developed non-hypercapnic hypoxemic respiratory failure in less than 72 h. In 28 intensive care units from France and Belgium with established experience in delivering NIV, 374 immunocompromised patients with PaO_2 less than 60 mmHg on room air, or respiratory rate greater than 30/min, or signs of respiratory distress, were randomized to receive NIV or conventional oxygen therapy. Of note, patients were stratified according to the cause of immune deficiency in two groups, one with hematologic malignancy or solid cancer, and one with solid organ transplant or long-term/high-dose immunosuppressive treatment. No difference was found between groups with regards to the primary endpoint, the mortality rate at 28 days after randomization (NIV 24.1% *vs.* oxygen 27.3%; 95% CI, −12.1 to 5.6; P=0.47). Secondary outcomes were also similar between the two groups: proportion of patients requiring endotracheal intubation (NIV 38.2% *vs.* oxygen 44.8%; 95% CI, −16.6 to 3.4; P=0.20), time to intubation, ICU-acquired infections, duration of mechanical ventilation, and length of stay in ICU and hospital. Also the analysis of the two pre-specified subgroups did not result in any significant difference. The conclusion of the investigators was that among immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure, early NIV compared with oxygen therapy alone did not reduce 28-day mortality.

Table 1 highlights design and results of this trial in comparison to the previous RCTs from Antonelli *et al.* and Hilbert *et al.*

This was a large and well conducted RCT assessing the early use of NIV. There was a high protocol adherence among institutions with expertise in delivering NIV and caring for immunocompromised patients. This trial also powered the primary outcome to reducing patient mortality in comparison to the trials performed by Antonelli and Hilbert *et al.* who focused on reducing the need for intubation. However, this RCT carries a few limitations, acknowledged by the investigators. In particular, the lower mortality rate than expected in the control group reduced the power of the study to find a significant difference in the primary outcome. Indeed, the trial was designed anticipating a mortality of 35% in the oxygen treated group, whereas the observed mortality rate was 27.3%. As a result, the possibility of drawing definitive conclusions and a clinically meaningful effect based on the study findings is limited.

The reasons of this low mortality rate may be given by a few considerations related to the management of immunocompromised patients. Practices have changed and the prognosis has improved over recent years. Furthermore, the centers involved in the study carry high level of expertise in the field of immunocompromised ICU patients and in NIV. The relationship between case volume and outcomes has been evidenced in this specific field (2). Importantly, the authors speculated that the low mortality rate was potentially due to the higher number of patients in the control group that were treated with heated and humidified high flow oxygen delivered by nasal cannula (HFNC) system compared to the NIV group (44% *vs.* 31%, P=0.01, respectively). The support provided by HFNC in the control group could have remarkably reduced the need of invasive mechanical ventilation, thus masking the potential efficacious effect of NIV in this patient population. HFNC, which has gained increasing clinical and scientific interest (26-47), can deliver up to 100% of heated and humidified fraction of inspired oxygen at a maximum flow rate of 60 L/min. This flow rate is significantly higher than the one delivered via nasal prongs or facemask, which is able to provide a maximum flow of 15 L/min. This limited flow rate is important given that patients with severe respiratory distress often require inspiratory flow rates ranging between 30 and 120 L/min. The consequence of this difference in required inspiratory airflow and provided flow rate is the dilution of the oxygen therapy with room air, so that the delivered FiO_2 is lower than the set FiO_2 (48). The high flow rates delivered by HFNC may partially overcome this issue. In addition, the high airflow delivered directly to the nasopharynx, improves carbon dioxide clearance and reduces dead space, thereby improving alveolar ventilation (29,41,48), and may also induce generation of positive end expiratory pressure (PEEP) (27,30,36,37). In

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Table 1 Comparison among seminal randomized controlled trials (RCTs) assessing the use of non-invasive ventilation (NIV) for hypoxemic respiratory failure in immunocompromised patients

Variables	Antonelli *et al.* (14)	Hilbert *et al.* (12)	Squadrone *et al.* (15)	Wermke *et al.* (19)	Lemiale *et al.* (25)
Setting	Single center, 14-bed general ICU	Single center, 16-bed general ICU	Single center, 2 hematology wards	Single center, hematology ward	Multicenter, 28 ICUs in France and Belgium
Study population	Adult	Adult	Adult	Adult	Adult
Criteria for acute hypoxemic respiratory failure	RR >35/min; PaO_2:FiO_2 <200 while breathing oxygen; active contraction of accessory muscles of respiration or paradoxical abdominal motion	Pulmonary infiltrates and fever; severe dyspnea at rest; RR >30/min; PaO_2:FiO_2 <200 while breathing oxygen	Bilateral pulmonary infiltrates; SpO_2< 90% on room air; RR >25/min; respiratory symptom duration <48 h	RR >25/min; PaO_2:FiO_2 <300 or SpO_2 <92% on room air	PaO_2 <60 mmHg on room air; RR >30/min, or labored breathing or respiratory distress or dyspnea at rest; respiratory symptom duration <72 h
Criteria for immunosuppression	Solid organ transplant recipients	Neutropenia after chemotherapy or bone marrow transplantation in hematologic cancers; organ-transplant recipients; corticosteroid or cytotoxic therapy for a non-malignant disease; acquired immunodeficiency syndrome	Hematologic malignancy and chemotherapy/bone marrow transplant	Allogeneic hematopoietic stem cell transplant	Hematologic malignancy; solid tumor (active or in remission for less than 5 years); solid organ transplant recipients; long-term (>30 days) or high-dose (>1 mg/kg/d) steroids, or any immunosuppressive drug taken in a high dosage or for more than 30 days
Number of patients	40 (interventional arm: 20; control arm: 20)	52 (interventional arm: 26; control arm: 26)	40 (interventional arm: 20; control arm: 20)	86 (interventional arm: 42; control arm: 44)	374 (interventional arm: 191; control arm: 183)
Control arm	Oxygen via Venturi mask	Oxygen via Venturi mask	Oxygen via Venturi mask	Oxygen via nasal insufflation or Venturi mask	Oxygenation modalities and the use of HFNC at clinician's discretion
Interventional arm	NIV via facemask; pressure support adjusted to obtain: (I) Vt =8–10 mL/kg; (II) RR <25 b/min; (III) disappearance of accessory muscle activity; (IV) patient comfort	NIV via facemask; pressure support adjusted to obtain: (I) Vt =7–10 mL/kg; (II) RR <25 b/min; (III) PEEP increased by 2 cmH_2O, up to 10 cmH_2O, until FiO_2 requirement ≤65%; FiO_2 for SpO_2>90%	CPAP via helmet; CPAP at 10 cmH_2O and FiO_2 50%	NIV via facemask; pressure support initially set to 15 cmH_2O; PEEP initially set to 7 cmH_2O; pressure support and PEEP adjusted according to patient tolerance and capillary blood gas analysis	NIV via facemask; pressure support adjusted to obtain: (I) Vt =7–10 mL/kg ideal body weight; (II) initial PEEP 2–10 cmH_2O; (III) FiO_2 and PEEP adjusted to SpO_2 ≥92%

Table 1 (*continued*)

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Table 1 (*continued*)

Variables	Antonelli *et al.* (14)	Hilbert *et al.* (12)	Squadrone *et al.* (15)	Wermke *et al.* (19)	Lemiale *et al.* (25)
Duration of treatment in interventional arm	On day 1, NIV continuously maintained until oxygenation and clinical status improved; subsequently, daily evaluation while breathing supplemental oxygen without ventilatory support for 15 min	NIV for at least 45 min and alternated every 3 h with periods of spontaneous breathing NIV resumed when arterial oxygen saturation <85% or dyspnea worsened	4-day periods consisting of at least 12 consecutive h/day of CPAP; at the end of each period, patients underwent a 6-h screening test during which they breathed through a Venturi mask with FiO_2 30%; if radiological evidence of pulmonary infiltrates, SaO_2 <95% or RR >25/min, patients returned to the assigned treatment for another 4-day period	NIV administered intermittently for at least 30 min every 3 h	NIV 60 min session every 4 h, for at least 2 days
Primary Outcome	Need for endotracheal intubation and mechanical ventilation at any time during the study	Need for endotracheal intubation and mechanical ventilation at any time during the study	Need of mechanical ventilation requiring ICU admission and, among patients admitted to ICU, number of patients who required endotracheal intubation for invasive ventilation	Difference in 100-day mortality	All-cause mortality within 28 days after randomization
Results	Reduction of number of patients requiring intubation in NIV *vs.* control group	Reduction of number of patients requiring intubation in NIV *vs.* control group	Lower number of patients who needed ICU admission for mechanical ventilation and lower intubation rate in CPAP *vs.* control group	No difference in 100-day mortality	No difference in 28-day mortality
Notes	Patients with cardiogenic pulmonary edema as the cause of respiratory failure were included in the study	–	–	Of 17 patients failing on control group, 16 crossed over to treatment group, which may have impaired analyses of outcomes	Study power was limited as the mortality in the control group resulted lower than predicted; a higher number of patients in the control group were treated with HFNC

ICU, intensive care unit; RR, respiratory rate; NIV, non-invasive ventilation; Vt, tidal volume; PEEP, positive end expiratory pressure; CPAP, continuous positive airway pressure; HFNC, heated and humidified high flow oxygen delivered by nasal cannula.

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healthy volunteers treated with HFNC with closed mouth and a flow rate of 60 L/min the measured PEEP was as high as 7.4 cmH_2O (30). Furthermore, the heated and humidified airflow delivered with HFNC may provide more comfort to patients requiring oxygen therapy (28,29,48). These potential benefits of HFNC should be studied in a systematic trial and compared to NIV, helmet CPAP and conventional oxygen therapy.

Some other limitations of the study may be related to the actual dose of NIV provided. First, the median durations of treatment were 8 h during the first 24 h, 6 h on day 2 and 5 h on day 3. At present we do not know whether longer durations of NIV would provide different outcomes. Previous studies in immunocompromised patients such as the one from Hilbert *et al.* (12) reported similar although slightly higher mean durations of treatment, with 9 h of NIV in the first day, and 7 h in the subsequent days. Second, the level of PEEP may play a significant role. As evidenced by the Editorial from Patel and Kress accompanying the study of Lemiale *et al.* (49), the physiologic goals of NIV in the treatment of acute hypoxemic respiratory failure rely on lung recruitment with proper use of PEEP and respiratory muscles unloading with addition of pressure support ventilation. Physiologic studies examining use of NIV in acute lung injury have suggested that a PEEP of at least 10 cmH_2O is required to significantly improve PaO_2:FiO_2 ratio with therapy (50). The protocol of Lemiale *et al.* allowed an initial PEEP between 2 and 10 cmH_2O, and then adjusted (together with FiO_2) in order to maintain the peripheral capillary oxygen saturation at 92% or greater. Even if at present it is unclear and difficult to estimate the optimal clinical PEEP setting during NIV, either too low or too high PEEP values could potentially have deleterious consequences. Furthermore, interface-related problems such as facemask leaks or poor patient tolerance may limit accurate titration of PEEP and pressure support ventilation, thus decreasing the efficacy of NIV delivered via facemask (49). Third, excessive NIV support may cause alveolar overdistension or alveolar recruitment and derecruitment, the two main mechanisms of ventilator-induced lung injury (VILI), which may exacerbate the already established injury in patients with acute respiratory failure (48). The possible role of NIV in contributing to VILI may hence provide another explanation for the lack of efficacy of NIV in immunocompromised patients. Interestingly, Carteaux *et al.* assessed expired tidal volume in patients undergoing NIV for *de novo* acute hypoxemic respiratory failure in a recent prospective observational study involving 62 patients in a single institution university medical ICU, showing that delivered tidal volumes are higher than expected (49). In particular, the median (interquartile range) tidal volume was 9.8 mL/kg predicted body weight (8.1–11.1 mL/kg), although the targeted tidal volume was 6–8 mL/kg predicted body weight. In this study, high tidal volume was independently associated with NIV failure, which occurred in 51% of the cases. In the sub-group of patients with PaO_2:FiO_2 of less than 200 mmHg a tidal volume of 9.5 ml/kg accurately predicted NIV failure with a sensitivity of 82% and a specificity of 87%. These data are remarkable with regards of the potential contributing role of high tidal volume during NIV to VILI. In Lemiale *et al.*'s investigation, the median expiratory tidal volumes were 8.8 mL/kg of ideal body weight on day 1, 9.1 on day 2 and 9.5 on day 3, respectively. Although there were no significant differences in tidal volumes according to NIV success *vs.* failure or between survivors and non-survivors, the study may have not been adequately powered to make these distinctions based on tidal volume, and the role of excessively high tidal volumes achieved during NIV may have been underestimated.

Also differences in patient populations may be one of the reasons for the different findings in Lemiale *et al.*'s trial with respect to previous studies. Their patients showed lower degrees of tachypnea compared to Antonelli *et al.* and Hilbert *et al.*'s studies (respiratory rate of 25–27/min *vs.* 35–38/min) suggesting a difference in severity of the acute condition.

Limitations of current knowledge and future directions

Where do the recent findings from Lemiale *et al.*'s study leave the clinician at the bedside caring for immunocompromised patients in the ICU? Several questions remain open:

(I) The role of HFNC alone or in combination with NIV (using HFNC in between NIV sessions) in this patient population will need further investigation. As mentioned above, the higher number of patients in the control group that were treated with HFNC system compared to the NIV group in Lemiale *et al.*'s study may have partially explained the lower-than-predicted mortality observed. The data from the recent FLORALI study report that in a post hoc adjusted analysis that included the 238 patients with severe initial hypoxemia (PaO_2:FiO_2 ≤200 mmHg), the intubation rate was significantly lower among patients who received high-flow oxygen than among patients in the other two

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groups (P=0.009) (46). A multicenter parallel RCT in four intensive care units assessing the role of HFNC *vs.* Venturi mask oxygen in immunocompromised patients with acute hypoxemic respiratory failure was published by the group of Lemiale and Azoulay. Patients were randomized to 2 h of HFNC or Venturi mask oxygen (51). The primary endpoint was a need for invasive mechanical ventilation or NIV during the 2-h oxygen therapy period. They found no significant difference between the two groups (15% with HFNC and 8% with the Venturi mask, P=0.36). None of the secondary end-points, which included comfort, dyspnea and thirst, differed significantly between the two groups. The authors concluded that in immunocompromised patients with acute hypoxemic respiratory failure, a 2-h trial with HFNC did not improve mechanical ventilatory assistance or patient comfort compared with oxygen delivered via a simple Venturi mask. However, this study was underpowered given the low event rate and use of a one-sided hypothesis only. Furthermore, this trial focused only upon the initial 2 h after ICU admission and thus the role of HFNC for longer periods of time remains to be assessed.

(II) With improving technology in the near future, NIV might be delivered with interfaces that minimize facemask leaks thus improving the efficacy of treatment and leading to better patient outcomes. Furthermore, our capability to control tidal volumes more accurately may increase, helping us avoid propagation of injury through VILI.

(III) The concern around the potential detrimental effects of delaying intubation in patients who receive NIV remains open. A recent secondary analysis of a prospective observational cohort study published by Kangelaris *et al.* analyzed data on 457 patients with acute respiratory distress syndrome. Of them 106 (23%) were not intubated at the time of meeting all other acute respiratory distress syndrome criteria. Non-intubated patients had lower morbidity and severity of illness than intubated patients; however, mortality at 60 days was the same (36%) in both groups (P=0.91). Of the 106 non-intubated patients, 36 (34%) required intubation within the subsequent 3 days of follow-up, and this late-intubation subgroup had significantly higher 60-day mortality (56%) when compared with both early intubation group (36%, P<0.03) and patients never requiring intubation (26%; P=0.002). The increased mortality in the late intubation group persisted at 2-year follow-up (52). However, the authors reported that there was no evidence that NIV modified the association between intubation and mortality, i.e., delaying endotracheal intubation through the use of NIV did not account for increased mortality.

Conclusions

NIV remains an attractive modality when caring for immunocompromised patient with acute hypoxemic respiratory failure, in light of its potential to avoid the complications of invasive mechanical ventilation. Further adequately powered trials will help us understand which patient subpopulations will benefit the most from each technique (HFNC, NIV or invasive mechanical ventilation), and to identify the most appropriate timing of application of these techniques.

The ongoing efforts towards optimizing the management of acute hypoxemic respiratory failure in immunocompromised patients keep us hopeful that the mortality of these frail patients will continue to decrease in the coming years.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Conservative versus liberal oxygenation targets for mechanically ventilated patients—a pilot multicenter randomized controlled trial

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Introduction

Panwar and colleagues recently reported the results of a prospective multicenter international interventional trial comparing two oxygenation targets in all-comer patients receiving invasive mechanical ventilation in ICU, namely a conservative (SpO_2 88–92%) versus a liberal target (≥96%), by accommodating FIO_2 (1). The rationale behind this was that no previous trial was done to compare different oxygenation goals in mechanically ventilated patients. Even though oxygen therapy is frequently used in the critical care setting, its goals are not well defined. The primary outcome was the area under curve of transcutaneous oxygen saturation (SpO_2). They included 104 patients in both groups and found that the primary end-point was significantly lower in the conservative than in the liberal group. From this result the authors concluded that reaching a conservative oxygenation target is feasible, which will serve for an upcoming large trial testing these two oxygenation levels.

We would like to split the present editorial into three sections. The first is about the pathophysiological rationale of the study. The second deals with the methodology and the results of the trial. The third will discuss its strengths and limitations.

Pathophysiological rationale

Two basic physiologic tenets are the background of this study, namely oxygen transport and oxy-hemoglobin dissociation curve. Blood oxygen transport to the tissues (TaO_2) is equal to cardiac output (L/min) × arterial content (CaO_2 in mL/100 mL). CaO_2 is equal to Hemoglobin concentration (G/L) ×1.34 mL/mL × SaO_2 (%) +0.0031 (/mmHg) × PaO_2 (mmHg). The oxy-hemoglobin dissociation curve displays the relationship of oxygen arterial saturation (SaO_2) to PaO_2. It is not linear throughout and two parts can be seen. Below PaO_2 55 mmHg/SaO_2 90% the relationship is linear with a deep slope. Above this threshold it is curvilinear and large changes in PaO_2 are associated with small changes in SaO_2. That means that from 95% to 100% SaO_2 the magnitude of PaO_2 change may widely range between 100 and 600 mmHg. Furthermore, $PaCO_2$ levels, blood pH and temperature are well known factors that shift the oxy-hemoglobin dissociation curve and these are frequently abnormal in the critical care setting. It is therefore complicated to hypothesize for a given patient the relationship between PaO_2 and SaO_2.

Oxygen therapy should balance risks and benefits of permissive hypoxemia and hyperoxemia due to supra therapeutic oxygen administration. The issues are first the threshold of oxygenation that should indicate the oxygenation supplementation and then the target oxygenation window, within which oxygen administration should be titrated further.

The risks of hypoxemia are cell oxygen deprivation in tissues like brain and heart. It should be mentioned that hypoxemia has a vasodilator effect in some regional

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circulations like kidney (2) but a vasoconstrictor effect in the pulmonary circulation.

Permissive hypoxemia can worsen an ongoing tissue hypoxia, due for example to a circulatory failure. Indeed, for SaO_2 less than 90%, small decrease in PaO_2 leads to major fall in SaO_2 and therefore in CaO_2 and hence TaO_2. Acute and chronic hypoxemia is associated with multiple pathophysiological pathways activation (hypoxic pulmonary vasoconstriction, activation of HIF1, ET-1, NFκB and arachidonic acid pathway) (3). Nevertheless, the threshold of life-threatening hypoxemia is not well defined and a value of PaO_2 of 55 mmHg is usually accepted. Interestingly, this value indicates long-term oxygen therapy in COPD patients.

On the other side of the spectrum, hyperoxemia can be associated with oxidative stress, ischemia-reperfusion lesions, absorption atelectasis (4). In patients with acute myocardial infarction, but without hypoxemia, 8 L/min pure oxygen supplementation was associated with larger infarct size as compared to no oxygen supplementation (5). In patients who had recovered from cardiac arrest restrictive oxygen use may be associated with some benefits to patient outcome (6). Furthermore, hyperoxemia might be harmful for two other reasons, which are clinically relevant.

First, hyperoxemia may result from the deliberate use of potentially harmful ventilator settings like higher tidal volume or higher positive end expiratory pressure.

Second, as previously mentioned, at high PaO_2 level marked drop in PaO_2 can be heightened because, due to the shape of the oxy-hemoglobin dissociation curve, SaO_2 will slightly change. So, important serious events altering gas exchange can be occurring without immediate warning to the clinician. Finally, previous attempts to supra maximize oxygen transport were associated with no (7) or even harmful (8) effect on patient outcome.

Given the inclusion criteria selected by the authors, the study investigated the impact of low or high oxygenation targets in patients under invasive mechanical ventilation with or without hypoxemia at the baseline. That means that the toxicity of lower or higher levels of oxygenation on one hand and the oxygen needs on the other hand are similar in any ICU patients.

The relationship of hypoxemia to death is well documented in ARDS patients (9). That does not mean that reverting hypoxemia would increase survival. The opposite was even true in the ARMA trial (10) where the lower tidal volume group had the worst hypoxemia but the highest survival. Indeed the paradigm in ARDS shifted from oxygenation target to prevention of ventilator-induced lung injury (11). The ARDSnet performed several high-quality trials by using oxygenation target, which was in the range of the conservative arm of present study (10). This target has been used in other large trials on ARDS by investigators not affiliated to the ARDSnet (12-14). In a recent trial on patients with acute hypoxemic respiratory failure and breathing spontaneously high-flow oxygen administered through nasal cannula was compared to oxygen delivered through a face mask and the oxygenation target was SpO_2 92% to titrate the rate of oxygen delivery in both groups (15). This same threshold was used in a trial on ventilator strategies done in the theatre in patients with normal lungs (16). To date, the BTS guidelines for emergency use of oxygen recommend the 94–98% SpO_2 window except for COPD patients (88–92%) (17), despite a low level of evidence.

Finally, two methodological issues are worth noting and are relevant to the present study. First, the accuracy of SpO_2 device to reflect SaO_2 in ICU patients is not so clear. In a single center study, very large variations between them were found (18). Second, in the perspective of a multicenter large trial the consistency across the blood gas analyzers should be checked.

Methodology and results of present study

In the study by Panwar *et al.*, concerning 103 patients, area under the curve (AUC) for SpO_2, the primary end-point, averaged 93.4% (95% CI: 92.9–93.9%) and 97% (96.5–97.5%) in the conservative and liberal group, respectively (P=0.0001). The mean AUC for PaO_2 was 70 [68–73] mmHg in the conservative arm and 92 [89–96] mmHg in the liberal arm. Furthermore, mean AUC for FiO_2 was lower in the conservative group [0.26 (0.25–0.28)] than in the liberal group [0.36 (0.34–0.39)]. In the conservative group, 14% of time were spent off the target versus 3% in the liberal group (P<0.001). Episodes of arterial desaturation (SpO_2 <86% for more than 5 minutes) were more frequent in the conservative group {1 [0–5] *vs.* 0 [0–0], P<0.001}. On the other hand, liberal group was exposed more frequently to hyperoxemia (defined as a SpO_2 >98% with FiO_2 >21%), with 22% of the SpO_2 readings meeting this criterion versus 4% (P<0.001). No significant difference in organ dysfunction or mortality was found between the two groups. In the predefined subgroup of hypoxemic patients (defined as a PaO_2/FiO_2 <300 mmHg at the time of inclusion), no differences in terms of survival or ventilator support duration were observed between the two strategies.

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Discussion of the results and strengths and limitations of the study

This is indeed the first study to investigate two oxygenation goals in critically ill patients receiving invasive mechanical ventilation.

The conservative strategy was most of the time successfully applied and no excess of morbi-mortality was reported. It supports larger RCT. Higher incidence of arterial desaturation was observed as expected. Jubran *et al.* previously found that only SpO_2 greater than or equal to 92% (or 95% for black patients) could guarantee PaO_2 greater than 60 mmHg (19). At the same time, the conservative goal was more difficult to reach. This reflects the use of relatively low FIO_2 in this study (despite the presence of at least 20% of patients with ARDS) and one can assume patient with normal lung function exhibits a "normal" SpO_2 when exposed to FiO_2 close to 0.21. It should be noted that almost 50% more arterial blood gases were performed in this group (P=0.04). This may reflect the loss of accuracy of SpO_2 at low values or the concern of clinicians facing low SpO_2.

The liberal group was exposed to SpO_2 greater than or equal to 96%. In terms of either mean SpO_2, PaO_2 or SaO_2 patients in the «liberal» group were within «normal» physiological values for healthy individuals. However, such levels are not recommended for patients with COPD or chronic respiratory failure and could lead to more harm in this population. Interestingly, there were twice more COPD patients in the conservative group (21% *vs.* 10%).

Hyperoxemia was defined as SpO_2 value of 99% or 100% and henceforth was part of the liberal target. In terms of PaO_2, patients in the liberal group experienced PaO_2 greater than 120 mmHg at 13% of the time points (*vs.* 3%, P<0.001). It should be noted that no upper alarm for SpO_2 was set, which might explain a bigger incidence of hyperoxemia in the liberal arm.

Intermittent hypoxemia, as in the sleep apnea syndrome, occurs at PaO_2 levels observed in the conservative arm. Seven-percent of the time points were with a PaO_2 less than 55 mmHg in the conservative group (versus 1% in the liberal group, P<0.001). Therefore, some patients in the conservative group might have experienced uncontrolled transient hypoxemia, for which chronic effects are known to be detrimental. These negative effects though preferred in case of ARDS over harmful effects of aggressive therapy as discussed above, might have a lower benefits-to-risk balance in other clinical situations.

On the other hand, hyperoxemia is not desired to avoid the potential risk of oxidative stress, notably. Most of the animal studies and the rare human studies reporting these risks were realized with supratherapeutic FiO_2 levels. Recent report of the Hyper2S study done in patients with septic shock demonstrated harmful effect in the hyperoxemia group (P Asfar *et al.* unpublished results). Patients in this group were exposed to a FiO_2 of 1 during one day. This translates for healthy human to a PaO_2 of at least 400 mmHg. The authors of the present article did not report such PaO_2.

Despite significant results in terms of mean AUC for SpO_2, SaO_2 and PaO_2, there was a large overlap between the two groups, which make results harder to analyze. As specified in the supplementary materials, the conservative group had in fact two targets: (I) SpO_2 90–92% for FiO_2 <50%; and (II) SpO_2 88–90% for FiO_2 ≥50%. This could explain the absence of clear difference between patients. It also highlights the variability in the measure of the SpO_2, which might be an argument to SpO_2-based oxygen delivery.

The relatively large inclusion criteria are both strength and a limitation of this study. The heterogeneity of patients reflects the "real life" patients. However, as stressed above, some specific populations (hypoxemic patients, COPD patients, patients with acute circulatory failure) might need a specific target.

Another limitation of the study is the large number of patients (69 pts for 357 pts screened) excluded due to treating physician lacking equipoise. Such an exclusion rate is worrisome and may have offset the advantage of large inclusion criteria. It also might reflect the fear of the clinicians to expose COPD patients to important amount of O_2 or expose healthy individuals to hypoxemia.

The possibility to alter the specified target by the treating physician reflects the bedside practice but also may blunt the effects of the studied targets.

Conclusions

The upcoming large RCT will probably answer most of the questions raised above. However, applying the same oxygenation target to any patient does not seem to go in the direction of a personalized medicine (20). As most of the trials challenging physiological targets (transfusion thresholds, mean arterial pressure goal), we might once again rediscover that "conservative" or "restrictive" management are not so easy to reach and, most of all, that one size does not fit all.

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Footnote

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Permissive hypoxemia/conservative oxygenation strategy: Dr. Jekyll or Mr. Hyde?

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Oxygen is one of the essentials required for sustaining life, which plays an important role in human medical history. It has become a routine therapy for critically ill patients, and the assessment and administration of oxygen in the ICU gained more and more attention (1,2). Both hypoxia and hyperoxia is related to adverse outcome. de Jonge *et al*. demonstrated that there was a U-shaped relationship between PaO_2 and in-hospital mortality, the lowest of the mortality being at PaO_2 values of 110–150 mmHg; mortality sharply increased both at PaO_2 values <67 and >225 mmHg (3). Nowadays, the "double-edged sword" character of oxygen is well established. On one hand, the hypoxia result in the imbalance between O_2 supply and requirements, which could induce tissue hypoxia and cell death. On the other hand, the presence of hyperoxia enhances reactive oxygen species (ROS) and oxidative stress, which cause alveolar and cell damage. The benefit/harm ratio of oxygen therapy is determined by the O_2 dose, exposure duration, and underlying diseases. To reduce the potential risks of hyperoxia, a lower oxygenation targets may be acceptable in critically ill patients. A tolerable low SaO_2 also termed as permissive hypoxemia/conservative oxygenation strategy. Generally, the permissive hypoxemia strategy aims for an SaO_2 between approximately 85% and 95%, which always use in the ARDS patients and preterm infants (4,5).

Recently, Panwar *et al*. present an intriguing pilot randomized, controlled, unblinded, international multicenter study in which they compared a conservative oxygenation strategy (aimed target SpO_2 88–92%) to a traditional, liberal strategy (aimed target SpO_2 96%) in the *Am J Respir Crit Care Med* (6). There were no significant between-group differences in any measures of new organ dysfunction, or ICU 90-day mortality. The study was well conducted with excellent adherence to study protocol and successful intervention. The authors concluded conservative oxygenation strategy is a feasible alternative to the usual liberal oxygenation strategy, while being effective in reducing exposure to hyperoxia.

However, some important points merit discussion. First, the concept of "permissive hypoxemia" is similar to the "permissive hypercapnia" or "permissive impaired peripheral perfusion" (4,7). To some extent, the adaption of cellular and organ may occur during hypoxemia that facilitates survival without increased harm. It has been acceptable maintaining normal physiology status could result in further injury compared to keep the permissive impaired physiological status in critically ill patients. Here, we stress the concept of permissive hypoxemia reflect the careful balance between the target SaO_2 and the ventilator toxicity required to achieve a higher SaO_2, not just a specific SaO_2 goal. Furthermore, the conservative oxygenation strategy/permissive hypoxemia therapy should be used in some selected patients who are with a high risk of hyperoxia, but not for all patients. Studies have shown hyperoxia is associated to poor outcome in the post-cardiac arrest, traumatic brain injury, and ischemic stroke patients. Permissive hypoxemia always works as a lung-protective strategy that aims to minimize the detrimental effects of the usual ventilatory support in ICU (8). Second,

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the purpose of permissive hypoxemia deserves clarification. Apparently, the permissive hypoxemia is used to avoid the harm of hyperoxia in clinical practice. So, the injury of hyperoxia should be well defined according to different patients. Study demonstrated the severe hyperoxia (PaO_2 >300 mmHg) but not moderate hyperoxia (101–299 mmHg) is related to bad outcome, and moderate hyperoxia (101–299 mmHg) was associated with improved organ function at 24 h in the cardiac arrest (9). Interestingly, there was no patients with severe hyperoxia (PaO_2 >300 mmHg) in the usual liberal oxygenation strategy group in Panwar' study, and the patients with PaO_2 >150 mmHg also was rare. In other words, the usual liberal oxygenation strategy might be enough to avoid a toxic dose of oxygen therapy. Most clinicians believed mild hyperoxia would provide a reservation of oxygen, and fear the potential risk of hypoxemia in the critically condition. The adverse and benefit effects of exposure to mild hyperoxia need further research to investigate. Third, permissive hypoxemia also could increase pulmonary artery pressure (through hypoxic pulmonary vasoconstriction) and subsequently cause right ventricular dysfunction (10,11). Therefore, it would be a dilemma to implement the permissive hypoxemia in the ARDS patients with acute cor pulmonale. We suggest the right heart function should be monitored and assessed in the implementation of permissive hypoxemia.

Another concern is the definition of hyperoxia in Panwar' study. Both arterial hyperoxia and high fraction of inspired O_2 is related to hyperoxia. The most commonly used threshold to define hyperoxia was PaO_2 >300 mmHg (12), which is related to poor outcome. On the other hand, the lung tissue is continuously and directly exposed to oxygen, so inspire high fraction of O_2 might also result in lung damage. "Hyperoxic acute lung injury (HALI)" was used to describe the pulmonary-specific toxic effects of O_2. The severity of HALI is directly proportional both to the PO_2 (particularly above 450 mmHg, or a FiO_2 of 0.6) and the duration of exposure (13). Therefore, the target of permissive hypoxemia is not only a low SaO_2 but also a low FiO_2. The arterial hyperoxia must result from high FiO_2, but high FiO_2 could not guarantee arterial hyperoxia. Furthermore, the high FiO_2 is required to maintain the acceptable SaO_2 in the severe ARDS patients after the optimization of mechanical ventilation, and permissive hypoxemia might be more relevant in this condition.

Another big problem of implementation permissive hypoxemia is how to avoid tissue hypoxia and keep the balance between DO_2 and VO_2. Systemic oxygen delivery (DO_2) is the product of the arterial oxygen content and cardiac output, and the SaO_2 would play a significant effect on arterial oxygen content before SaO_2 reach to 100%. So, the relationship between DO_2 and VO_2 should be carefully evaluated during the implementation of permissive hypoxemia. The presence of normal central venous oxygen saturation (>70%), central venous-to-arterial CO_2 difference (<6 mmHg), lactate (<2 mmol/L) and central venous-to-arterial CO_2 difference/arterial-central venous O_2 difference ratio (<1.23) indicate the adequacy of DO_2 (14). The dynamic assessment of these related parameters would be useful to adjust the target of SaO_2 during permissive hypoxemia. In addition, the manipulate sedation, hemoglobin and cardiac output is also helpful to guarantee global oxygen delivery during the conservative oxygenation strategy (15).

Generally speaking, oxygen therapy should be a goal-directed, and early monitoring of both pulse oximetry and arterial blood gases is advised. Permissive hypoxia is one part of the oxygen administration strategy. Although the Panwar' study supported the feasibility of permissive hypoxia, but the evidence still is lacking in terms of the efficacy (16). Recently, the UK and Australian Benefits of Oxygen Saturation Targeting (BOOST) II trials showed an oxygen saturation target of 85% to 89%, rather than 91% to 95%, may increase the risk for death or disability at 2 years corrected age in infants born before age 28 weeks (17). The potential harm of hypoxia should be careful evaluated based on the pathological and physiological conditions, and it should be reminded that the benefit of permissive hypoxia is derived from the reduction of hyperoxia injury.

In conclusion, clinical evidence supporting permissive hypoxemia is not currently available and it will be important to carefully evaluate the risks and benefits of permissive hypoxia before proceeding to efficacy and effectiveness trials. Choosing the right therapeutic target and right patients is the key to make the permissive hypoxia strategy become Dr. Jekyll but not Mr. Hyde. So, we suggest future studies of permissive hypoxia should focus on the severe ARDS patients with high FiO_2 but not in critically ill patients with regular mechanical ventilation.

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Footnote

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From Berlin to Kigali: the sobering journey of acute respiratory distress syndrome

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What do Berlin, Kigali, and acute respiratory distress syndrome (ARDS) have in common? Berlin is the capital of Germany, brimming with attractiveness, science, culture, and a great lifestyle after the re-unification 25 years ago. Kigali is the largest city in Rwanda as well as its capital since the country's independence in 1962, located at an altitude of 1,560 m. ARDS is characterized by dysregulated inflammation, inappropriate accumulation of leukocytes, uncontrolled activation of coagulation, and alveolar barrier disruption (1), often resulting in a life-threatening impairment of pulmonary gas exchange with hypoxemia, hypercapnia, and respiratory acidosis. The main causes of ARDS are direct (pneumonia, aspiration of gastric content) or indirect injuries (sepsis, massive transfusion, multi-trauma, peritonitis, pancreatitis). In European countries, the incidence of ARDS was estimated to be 50 cases per 100,000 person years, corresponding to approximately 40,000 cases per year for a country like Germany (2). ARDS is often associated with multiple-organ failure. A broad scenario of acute interventions for ARDS therapy have been investigated and recommended in recent years, but evidence that all these measures can decrease mortality is still limited (3). Mortality remains as high as 40–50% in major series (4).

In 1994, a European-North American consensus conference introduced a 'simple' catalogue for the definition of ARDS and, at the same time, a differentiation from acute lung injury (ALI) was carried out as follows: ratio of arterial oxygenation to fractional inspiratory oxygen concentration (PaO_2/FIO_2-ratio) <200 (ALI <300), bilateral radiographic opacities without evidence for (exclusively) cardiac origin, acute onset (5). A presence or level of positive end-expiratory pressure (PEEP) was not addressed. In the following years, increasing activities in basic and clinical science in terms of pathophysiology, inflammation cascades, epidemiology, and the (deleterious) effects of mechanical ventilation to the injured lung were observed. Simultaneously, the critique on the 'simple' ARDS definition grew: the accuracy of the assessment of ARDS was seen as limited and the absence of a mandatory PEEP level for the classification of oxygenation impairment was criticized.

In 2011, during the Annual Congress of the European Society of Intensive Care Medicine in Berlin, an expert group created a new definition of ARDS (6). The main changes were: (I) a recommendation of three levels of three categories based on the degree of hypoxemia, whether mild, moderate or severe. Consequently, the term 'ALI' went 'overboard'; (II) the onset within 1 week of a known insult; (III) a minimum level of PEEP (≥5 cm H_2O); and (IV) an objective evaluation to help rule out hydrostatic edema (e.g., echocardiography). The new Berlin definition was evaluated on a cohort of >3,000 patients and found to be valuable.

As it turned out, even the Berlin definition found critics, but on a high intellectual and somewhat exaggerated level (7). On the other hand, thinking outside the high-income box, a more severe objection regarding the validity of the Berlin definition comes from Kigali, Rwanda. Riviello and co-workers (8) estimated the incidence and outcome of ARDS at the university teaching hospital at Kigali. They screened every adult patient in the hospital for

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6 weeks, and collected data on demographics and ARDS risk factors, predominantly by lung ultrasonography. The first (unsurprising) result was that the Berlin definition could not be applied in most patients due to the inaccessibility of mechanical ventilators, arterial blood gas diagnostics, and chest radiography. Consequently, the authors had to modify the ARDS definition to a Kigali version: the requirement of PEEP was deleted and a PaO_2/FIO_2 ratio was replaced by a SPO_2/FIO_2 ratio (9) using pulse oximetry (hypoxemia cut-off ≤315). Cardiac function was assessed by anamnesis or (when available) by echocardiography. The further main results were that 42 patients (median age 37 years) of 1,046 hospital admissions (4%) met the Kigali criteria for ARDS, 39% of ARDS patients were admitted to the ICU, and the mortality was 50%. The medico-political message of this important scientific contribution is that the Berlin definition is not applicable or is likely to underestimate the incidence of ARDS in low-income countries that represent a large part of the world and, furthermore, may result in estimates of only 'treated incidence' in high-income countries.

The study by Riviello *et al*. (8) poses severe reflections and some 'meta-questions':

- Is it possible, in the era of increasing high-tech medicine, to define diseases and/or assess grades of disease severity with validity and accuracy throughout the world when technical devices, lab values, and 'sophisticated' measurements are necessary, but not available to all?
- Science claims regarding the worldwide compatibility of results, cooperative projects, guidelines, and exchange of scientific data by international journals, symposia, and workshops: is it an illusion that scientists always speak about the same topic?
- Do we have to accept that first-world medicine (from high-income countries), second-world medicine (from advanced developing countries), and third-world medicine (from low-income countries) involve such different bases of scientific and clinical medicine that a 'true' cooperation is in far future?

Some conclusions or challenges for future global studies (10) can be drawn or postulated: on the one hand, different definitions of diseases or the severity of diseases around the world will counteract the globalization of science, which is necessary and unstoppable. On the other hand, it is not possible to work with definitions not applicable in parts of the world, or, when applied, producing invalid results. Where is the compromise and how can we go on? The Kigali study is a landmark study for a global approach to respiratory science and medicine: (I) it places the focus on daily life circumstances in a resource-constrained country with typical impacts for diagnosis and therapy, which are far away from the standard of industrialized countries; (II) the study is an important step for the improvement of systematic health technology trials (i.e., investigations on medical informatics systems) (11), which are necessary to understand (and improve) pathways of care in countries with a relatively weak health infrastructure and limited healthcare; (III) although the Kigali modification of ARDS requires validation before widespread use, there is no doubt that scientists, clinicians, and healthcare specialists are called up to start projects and to stimulate further cooperation in reflecting on and refining an ARDS definition that can be used in all high-income and low-income countries.

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Footnote

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The Kigali modification of the berlin definition: a new epidemiological tool for ARDS?

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We read with great interest the paper by Riviello *et al.* (1) in which they used an "adjustment" of the Berlin definition, the so called "Kigali modification", to estimate the incidence and outcomes of acute respiratory distress syndrome (ARDS) at a Rwandan referral hospital by the enrollment of every adult patient admitted for hypoxia (saturation less than 90%) throughout a 6-week period. According to the Kigali modification, ARDS was defined without the need of positive end-expiratory pressure, with the presence of bilateral opacities at chest radiograph or lung ultrasound and hypoxia was defined with a cutoff of SpO_2/FIO_2 less than or equal to 315. The study by Riviello *et al.* (1) interestingly points at a limitation of the Berlin definition, that is the real difficulties in a correct estimation of ARDS incidence in developing countries, taking into accounts differences in resource availability and especially in capacity for positive pressure ventilation and ICU beds.

In keeping with this contention, recent evidence (2) underscores that the global impact of ARDS itself is difficult to estimate due to demographic, economic and health care system differences among developed and developing countries. Moreover, risk factors for ARDS may differ between high and low income countries (3). While the higher percentage of traumatic and infectious disease in resource-poor settings may increase ARDS incidence, the lack of critical care resource may signify that critically ill patients die before the development of ARDS (4). Discrepancies in definition criteria [American Consensus Conference -AECC (5) *vs.* the Berlin Definition (6)] may aggravate objective difficulties in estimating ARDS incidence, especially in the developing world. In a multicenter, prospective cohort study (7), enrolling 773 patients admitted to 45-ICUs in Brazil over a 2-month period and requiring non invasive or invasive ventilation, ARDS was diagnosed in 31% of the patients according to the Berlin definition. In 4 Argentine ICUs, Estenssoro *et al.* (8) reported an incidence of ARDS of 7.7% of all ICU patients (3,050 adult patients admitted over a 15-month period) according to the AECC criteria. Finally, in a 15-month prospective, observational study, enrolling 7,033 patients in 14 ICUs in Brazil (9), 130 (1.8%) met the Berlin criteria for ARDS. In this context, the Kigali modification of the Berlin definition may help to overcome these difficulties by adapting the ARDS definition to the existing health care system in the developing world. On a conceptual basis, the goal of the Kigali modification was to avoid the underestimation of ARDS incidence in these countries and to obtain an estimate of the actual incidence (and not of the "treated incidence"). The low-availability of positive pressure ventilation and ICU beds led to "eliminate" the need of positive pressure ventilation in the Kigali modification and the scarcity of arterial blood gases and radiographs resulted in the use of SpO_2/FIO_2 and lung ultrasound, respectively.

Also in the developed world, discrepancies in ARDS

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occurrence still exist, especially between USA and Europe (2). In a retrospective analysis of patients admitted over a 8-year period [2001–2008] in a US county (Olmsted County, Minnesota, USA), an incidence of ARDS of 33.8/100.000 was reported (10), while in an extensive review of epidemiological studies performed after 2000, the ARDS incidence in Europe ranged from five to eight cases/100,000 (11). The results of the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) have been recently published (12). This investigation, which was an international, multicenter, prospective cohort study, was undertaken to assess the ICU epidemiology and outcomes from ARDS (as well as to evaluate clinical recognition of the disease and its management). One of the strengths of this study was that the patients were enrolled from all over the world, in the same period of 4 consecutive winter weeks (February–March 2014 in the Northern hemisphere and June–August 2014 in the Southern hemisphere). The overall incidence of ARDS was 10.4% of ICU admission and 23.4% of all patients requiring mechanical ventilation. Geographic variations were confirmed, with Europe having an incidence of 0.48 cases/ICU bed over 4 weeks; North America, 0.46; South America, 0.31; Asia, 0.27; Africa, 0.32; and Oceania, 0.57 cases/ICU bed per 4 weeks. Taking into account that the Berlin definition was adopted for all cases and the low availability of ICU beds in the developing world, it is conceivable to suppose that ARDS was underestimated in low-income countries. In other worlds, the results of the LUNG SAFE study strengthens the rationale for the Kigali modification of the Berlin definition.

However, the innovative and challenging investigation by Riviello *et al*. (1) encourages some reflections and stimulates some questions.

When the Berlin definition was elaborated, three criteria were fulfilled: feasibility, reliability and validity (13). Concerning the Kigali modification, feasibility seems to be met since diagnostic tests and/or clinical data (chest radiographs/lung ultrasound and SpO_2) are routinely used by clinicians in hospital settings in low-income countries. The term reliability indicates observer agreement on case identification but this criterion has still to be assessed with Kigali definition. Similarly, validity has to be proven, and especially the "so called" predictive validity, that is the ability to stratify patients by prognosis or response to therapy. Moreover, though each of the three pieces of the modification has been validated previously, the whole modification has not. All these methodological/technical limitations make the results of the study by Riviello *et al*. difficult to be compared to other studies. Their findings come from a small single center (in one country in sub-Saharan Africa) in one rainy season and indicate an hospital screening, while most previous studies screened intubated ICU patients.

Nevertheless, the clinical need to "adapt" to Berlin definition of ARDS to resource-constrained areas of the world can not be ignored and the Kigali modification may represent a practical response. Thus, its validation should be encouraged and further studies in other resource-constrained settings should be performed in order to assess reliability and validity of Kigali modification.

The aim of a disease definition has the same clinical importance all over the world, that is to facilitate case recognition and better match treatment options to severity.

A clinical, challenging question arises: is one definition for ARDS enough for developed and developing countries or should different "geographic" definitions for the same disease be used for a proper recognition and a correct estimate of its incidence?

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Acetazolamide use in severe COPD exacerbations requiring invasive mechanical ventilation: impact on duration of mechanical ventilation

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We read with interest the article titled "*Effect of Acetazolamide vs. Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial*" by Faisy *et al*. (1) where the authors have and colleagues randomly assigned patients with chronic obstructive pulmonary disease (COPD) who required invasive mechanical ventilation to receive either acetazolamide 500 mg intravenously twice daily (1,000 mg if loop diuretics were also prescribed) or matching placebo up to 28 days. A total of 382 patients with COPD who were expected to receive mechanical ventilation for more than 24 hours to acetazolamide (500–1,000 mg, twice daily) or placebo, administered intravenously in cases of pure or mixed metabolic alkalosis. The main results were: among 382 randomized patients, 380 [mean age, 69 years; 272 men (71.6%); 379 (99.7%) with endotracheal intubation] completed the study. For the acetazolamide group (n=187), compared with the placebo group (n=193), no significant between-group differences were found for median duration of mechanical ventilation (–16.0 hours; 95% CI, –36.5 to 4.0 hours; P=0.17). For secondary outcomes, there is no difference in duration of weaning off mechanical ventilation (–0.9 hours; 95% CI, –4.3 to 1.3 hours; P=0.36), in changes of minute-ventilation (–0.0 L/min; 95% CI, –0.2 to 0.2 L/min; P=0.72), or partial carbon-dioxide pressure in arterial blood (–0.3 mmHg; 95% CI, –0.8 to 0.2 mmHg; P=0.25). However, the authors observed a significant daily changes of serum bicarbonate (between-group difference, –0.8 mEq/L; 95% CI, –1.2 to –0.5 mEq/L; P<0.001), in the number of days with metabolic alkalosis (between-group difference, –1 days; 95% CI, –2 to –1 days; P<0.001) and significantly increased in the PaO_2:FIO_2 ratio in the acetazolamide group's. Other secondary outcomes also did not differ significantly between groups.

The authors concluded that among patients with COPD receiving invasive mechanical ventilation, the use of acetazolamide, compared with placebo, did not result in a statistically significant reduction in the duration of invasive mechanical ventilation.

Several hypotheses can be advanced to explain the inefficacy of acetazolamide to shorten the duration of mechanical ventilation in this study.

First, this inefficacy may be related to pharmacokinetic reasons. In fact, there are several isoforms of human carbonic anhydrase, and some may be more inhibited than others by ACET, which may complicate the reversal of metabolic alkalosis (2-4).

Second, several factors as serum chloride level and co-administration of furosemide or systemic steroid can interfere with ACET pharmacokinetics (5). Despite that in the study performed by Faisy *et al*. (1), co-treatments with loop diuretics, glucocorticoids, β2-agonists or catecholamines, were used in the same proportion in the two groups, theses therapeutics can interfere with ACET pharmacokinetics and decrease ACET effectiveness.

Third, the optimal dosage of acetazolamide to be administered to alkalotic COPD patients is unclear. The results of a recent study (6) suggest that higher doses of

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acetazolamide (>1,000 mg daily) are necessary to induce a substantial increase in minute ventilation and hence a decrease in $PaCO_2$ in alkalotic mechanically ventilated COPD patients. Moreover, this last study (6) suggests that the increase in minute ventilation following the administration of acetazolamide is obtained at the price of an increase in respiratory rate rather than tidal volume, whatever the ventilatory mode.

Fourth, a limitation of Faisy *et al*. (1) study is the presence of mixed metabolic alkalosis in most patients. In fact, the lack of acetazolamide respiratory effect may be due to the fact that many of the patients had a degree of metabolic alkalosis too mild for the intervention.

Fifth, although the two groups included in this study (1) have the same respiratory characteristics with the same forced expiratory volume in the first second of expiration (FEV1) and the same forced vital capacity (FVC), the poor mechanic capacities in severely flow-limited COPD patients may explain why the reversal of the depressive metabolic stimulus of the respiratory drive did not induce an increase in minute ventilation and thus, did not make weaning from ventilator support easier (4).

Sixth, the ACET induces a metabolic acidosis which stimulates the respiratory neural-driving leading to a hyperventilation with polypnea. This polypnea will significantly increase the workload of respiratory muscles and shortens the time of the respiratory cycle with its two components inspiratory and expiratory. As consequence, respiratory and/or limb muscle dysfunction, which are frequently observed in COPD patients will be increased by ACET prescription.

Seventh, as detailed by authors (1) the study may have identified a clinically important benefit of acetazolamide for the primary end point that did not demonstrate statistical significance because of a possible lack of power. In fact, the lack of statistical significance may be due to an underpowered study because of fewer-than-expected patients who received the treatment (more than 20% of patients in each group did not receive the assigned treatment because of lack of metabolic alkalosis or temporary contraindications. Moreover, despite it did not the reach statistical significance, the difference between-group in median durations of invasive mechanical ventilation was clinically considerable (16 hours). In fact, this last trial was prospectively powered to detect a 15% difference in the invasive ventilation duration, considered clinically relevant in light of the usual duration of intubation in these patients. However, the observed median durations of invasive mechanical ventilation in the placebo and acetazolamide groups were lower than anticipated for statistical power, complicating the study interpretation. This means that the 10% reduction of invasive mechanical ventilation by acetazolamide could have reached statistical significance if the study was designed to detect such a difference.

Finally, we found that this recent study, confirms the results of two retrospective, case-control studies (4,7) published on the same subject. The first study was published on 2010 (7), in this study, 26 intubated COPD patients with mixed metabolic alkalosis were compared with a historical control group (n=26) matched for serum bicarbonate, arterial pH, age, and severity of illness at admission to ICU. ACET administration (500 mg intravenously) was monitored daily according to arterial blood gas analysis from readiness to wean until extubation. The main results of this study were Patients with ACET treatment significantly decreased their serum bicarbonate (P=0.01) and arterial blood pH (P<0.0001), increased their PaO_2/FiO_2 ratio (P=0.04), but did not change their $PaCO_2$ (P=0.71). Compared with matched controls, administration of ACET did not improve arterial blood gas and respiratory parameters except PaO_2/FiO_2 ratio (P=0.03). The use of acetazolamide, compared with placebo, did not result in a statistically significant reduction in the duration of invasive mechanical ventilation. Moreover, extubation success rate was not significantly different between groups, and causes of reintubation were comparable.

The second study was more recently published (on 2015) (4). It is Retrospective pair-wise, case-control study with 1:1 matching. Patients were defined as cases when they had received acetazolamide (500 mg per day) and as controls when they did not received it. Patients were matched according to age, severity on admission (pH, PaO_2/FiO_2 ratio) and SAPSII score. This study included 72 patients equally distributed between the two studied groups. There were no differences between baseline characteristics of the two groups. Concomitant drugs used were also not significantly different between two groups.

The main results of this study were mean duration of mechanical ventilation was not significantly different between ACET(+) and ACET(–) patients (10.6±7.8 and 9.6±7.6 days, respectively; P=0.61). The use of ACET was associated with a significantly decreased serum bicarbonate, arterial blood pH, and $PaCO_2$ levels. Moreover, authors did not found any significant difference between the two studied groups in terms of ICU length of stay (LOS). ICU mortality was also comparable between ACET(+) and ACET(–) groups

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Table 1 Impact of ACET use in severe exacerbation of chronic obstructive pulmonary disease requiring invasive mechanical ventilation

Study	Type of study	Number of patients included	Dose of ACET (mg/day)	Effect of ACET use on duration of mechanical ventilation	Effect of ACET use on serum bicarbonate	Effect of ACET use on PaO_2/FiO_2 ratio
Faisy *et al*., 2010 (7)	Case-control study	26	500	Not significantly improved	Significantly decreased	Significantly improved
Bahloul *et al*., 2015 (4)	Case-control study	72	500	Not significantly improved	Significantly decreased	Not significantly improved
Faisy *et al*., 2016 (1)	Randomized placebo-controlled trial	380	1,000	Not significantly improved	Significantly decreased	Significantly improved

(38% and 52%, respectively; *P*=0.23). *Table 1* summarizes the impact of ACET use in severe exacerbation of chronic obstructive pulmonary disease requiring invasive mechanical ventilation in all published studies (1,4,7).

In summary, we can conclude that in severe exacerbation of COPD requiring intensive care admission and invasive mechanical ventilation, metabolic alkalosis occurs frequently in this group of patients who frequently receive therapies for cardiac and respiratory failures (steroids, diuretics, etc.). This disorder may depress central respiratory drive leading to hypoventilation and thus, hampers the weaning process. Despite that Acetazolamide, is used to reverse metabolic alkalosis after proper fluid loading and potassium supplementation, all published results of ACET in this specific condition suggests that systemic ACET therapy in this specific condition is not helpful to reduce the duration of mechanical ventilation and to make the weaning process easier (1,4,7). However, it is possible that the use of ACET can be efficient in a subgroup of patients. Thus, further studies are needed to evaluate the effect of ACET on ventilator weaning process in critically ill COPD patients requiring mechanical ventilation.

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Footnote

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Intraoperative mechanical ventilation in patients with non-injured lungs: time to talk about tailored protective ventilation?

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It is a well-established concept that general anaesthesia can impair lung function postoperatively, even in subjects with healthy lungs (1), and mechanical ventilation itself is considered to play a major role in contributing to such dysfunction. Mortality after surgery was found to be higher than expected (2), with postoperative pulmonary complications (PPCs) having a relevant impact on outcome (3,4). Following these epidemiological findings, several research groups aimed at identifying modifiable risk factors associated with PPCs, in order to plan mitigation strategies to reduce the incidence of such complications and improve patients' outcome. Among the others, several specific ventilation strategies have been found to be associated with a lower risk of developing PPCs. However, due to the low number of observed events, it is difficult to achieve a definitive answer on optimal intraoperative ventilation strategy to minimize the postoperative incidence of adverse events (5). In fact, general anaesthesia is nowadays considered as a safe procedure with a relatively low incidence of complications (6). The general tendency of the last decade was to translate the concept of "protective mechanical ventilation" borrowed by the critical care setting to non-injured lungs in operating room or intensive care and found to influence clinical outcome (7-9).

Several randomized controlled trials (RCTs) have investigated the role of tidal volume, PEEP and recruitment manoeuvres, both separately (10) or as bundles of multiple interventions (11). Even though RCTs are the gold standard to build high quality evidence, results are still not univocal. Moreover, the number of subjects that have to be included in RCTs to achieve an acceptable statistical power is high, also when predictive scores are used to screen patients and include those at higher risk for PPCs (5,12). Therefore, it is rather difficult to perform secondary analyses to identify subgroups of patients that can benefit from specific ventilation strategies, and researchers have few methodological options: designing dedicated trials for specific groups (i.e., in obese patients), pooling individual data from several RCTs (13), or analysing large retrospective databases. The latter strategy is the weakest in terms of scientific robustness, but has the advantage of being able to collect very large datasets, especially in centres using centralized automated collection of clinical data for research or administrative purposes. Definitive evidence is seldom obtained by retrospective data analysis, but several findings can be inferred and interpreted to improve the knowledge or to plan further prospective trials.

In a paper recently published on the *British Medical Journal*, Ladha and collaborators (14) analysed retrospectively a large hospital based registry study in three hospitals in Massachusetts, United States, including a total of 69,265 consecutive patients that underwent non-cardiothoracic surgery between January 2007 and August 2014. The principal outcome measure was the incidence of PPCs, defined as a composite endpoint combining several severe respiratory complications. The analysis was carried out at two stages: a first retrospective cohort comparison between patients that did or did not receive a protective ventilation strategy, followed by a secondary analysis on the effect of PEEP, tidal volume, plateau pressure and driving pressure as risk modifiers for the development of PPCs. In the retrospective threshold-based analysis, the authors

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essentially confirmed what was found by the majority of the prospective trials, namely that the lowest incidence of PPCs was observed with a protective ventilation combining PEEP ≥5 cmH_2O and tidal volume ≤10 mL/kg predicted body weight to achieve a plateau pressure lower than 30 cmH_2O. The results were confirmed when using propensity score matching, and the observed reduction in observed events was around 10%. In the secondary analysis, the authors found a positively skewed distribution of the tidal volume and plateau pressure, and a bimodal distribution of PEEP, with 0 and 5 cmH_2O representing the most common settings. The latter finding suggests that most clinicians tend to apply PEEP on a standard basis, with no tailored titration. It should also be remembered that many operative room ventilators are unable to deliver an actual PEEP of 0 cmH_2O, but rather a 2-3 cmH_2O achieved PEEP due to technical characteristics of the ventilator (6,8), and that this technical limit has been overcome only in few very recent machines. The multivariable logistic regression analysis showed that lower plateau pressure and moderate PEEP levels were associated with the better outcome. Driving pressure had a role comparable to that of plateau pressure, but in the study population the low variability in PEEP makes driving and plateau pressure highly interconnected. Surprisingly, no independent effect of tidal volume was observed. This finding suggests that the harmful effect of tidal volume dynamic strain is mediated by an increase in plateau pressure linked to lung compliance, possibly reflecting lung stress. This is a relatively innovative concept in intraoperative mechanical ventilation, that might reflect what has been recently observed in the ventilation of the injured lung (15). Moreover, the risk of developing PPCs increased when plateau pressure was higher than 16 cmH_2O, suggesting that the threshold of induction of lung injury in healthy lungs could be lower than expected.

The main limit that hampers the interpretation of the results, as mentioned by the authors themselves, is that the whole analysis relies on data initially collected for administrative rather than research purposes. Many of the potential confounding factors were thoroughly tested, including the role of patient clustering due to different caregivers, other factors, like the reliability of outcome data reporting, were impossible to check. The authors used multiple imputations to deal with missing data points, including a quality check to test whether the results changed excluding imputed values. Once seen very rarely in biomedical research, multiple imputation methods are gaining acceptance among researchers when used cautiously in large datasets (16). Despite the intrinsic limits of the retrospective study design and the recourse to sophisticated statistical models, the authors were careful in interpreting the results and tried to compensate most of the potential sources of bias, at least when technically feasible. These findings are substantially in line with the findings of most recent meta analyses, concluding that a protective strategy based on low tidal volume and moderate PEEP improves outcome (7,13). However, a recent article published by the *British Journal of Anaesthesiology*, showed that low tidal volumes and low PEEP were associated with an increased mortality (17). Thus it is difficult, in such retrospective studies, to discriminate whether a specific ventilation setting was a deliberate choice a priori or rather a strategy to overcome an intraoperative gas exchange impairment. Surprises sometimes arise from randomized trials: this is the case, for instance, of the PROVHILO study (10), that found no role of high PEEP alone in preventing PPCs, suggesting that the advantages of protective ventilation found by Futier *et al*. (11) were probably due to the tidal volume. In conclusion, actual evidence coming from RCTs, observational prospective and retrospective data analysis, as well as individual data meta-analysis suggest that protective mechanical ventilation surgery should include: (I) low tidal volume targeted to 6–8 mL/kg predicted or ideal body weight; (II) plateau pressure of the respiratory system maintained below 16 cmH_2O, as much as possible; (III) low levels of PEEP equal or lower than 5 cmH_2O, without recruitment manoeuvres; (IV) PEEP between 5 and 10 cmH_2O should be considered in patients with body mass index higher than 35 kg/m^2, laparoscopy surgery in Trendelenburg position and with a duration of surgery longer than 4 h. In case of oxygen desaturation, after excluding possible common causes like endotracheal tube misplacement or secretions in the airways, it is suggested to increase inspiratory oxygen fraction up to 70% and then perform a recruitment manoeuvre with non-invasive or invasive hemodynamic continuous monitoring. However, we agree with Ladha *et al*. (14) that a universal threshold of protectiveness, applicable to every patient, cannot be identified. All the efforts should be made to achieve an acceptable gas exchange avoiding excessive delivery of tidal volume leading to increased plateau and driving pressures. Further studies are necessary to identify the optimal ventilator settings for specific subgroup of patients. In particular, the role of patient-tailored PEEP setting, ventilation in obese patients as well as those undergoing laparoscopic surgery seem to be of particular interest. The more the knowledge advances,

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the benefits that can be achieved by further modifying intraoperative ventilation seems to be smaller: it is now the time to study broader interventions and bundles covering both the preoperative and the postoperative care of surgical patients.

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Footnote

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One more brick in the wall of protective ventilation in surgical patients

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Provenance: This is a Guest Commentary commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, China).

Abstract: On June 14, 2015, Ladha and colleagues published an article in the *BMJ* entitled "Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study", which investigated the effects of intraoperative protective ventilation on major postoperative respiratory complications. This study used data of over 69,265 patients in order to investigate patients over the age of 18 who underwent a non-cardiac surgical procedure between January 2007 and August 2014 and required general anesthesia with endotracheal intubation. The investigators found that intraoperative protective ventilation was associated with a decreased risk of postoperative respiratory complications. This study raises important questions about the ventilatory management of surgical patients.

Keywords: Mechanical ventilation; tidal volume; positive end expiratory pressure (PEEP); surgery; postoperative pulmonary complications (PPC)

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Driven by clinical and experimental studies, strategies of protective ventilation combining low tidal volume, low plateau pressure, and application of positive end expiratory pressure (PEEP) have gained widespread acceptance in intensive care units, especially for patients suffering from the acute respiratory distress syndrome (ARDS) (1). However, recent meta-analyses suggest that lower tidal volumes are protective not only during long-term ventilation in critically ill patients with ARDS (2), but also in short-term ventilation during general anesthesia for surgery (3). Indeed, the use of protective ventilation in surgical patients could reduce the incidence of postoperative pulmonary complications (PPC), a condition associated with increased length of stay and mortality in this group of patients (4,5).

In order to limit the risk of ventilator-induced lung injury (VILI), a number of reviews suggested that intraoperative mechanical ventilation should consist of low tidal volume to avoid volutrauma, moderate level of PEEP and periodic lung recruitment maneuvers to avoid atelectrauma and low plateau pressure to prevent barotrauma (6-8). At the cellular level, physical stimuli from mechanical ventilation are transformed into chemical signals, resulting in release of pro-inflammatory and anti-inflammatory mediators by means of direct cell injury or indirect activation of cellular signaling pathways (9). Some mediators may promote local effects such as pro-apoptotic or pro-fibrotic actions, whereas others act as homing molecules recruiting local and remote immune cell populations (10). These local effects as well as their immunological consequences are summarized by the term "biotrauma" (11).

From a physical perspective, the VILI process must be related also to the energy transfer from the ventilator to the lung. Due to the phenomenon of hysteresis the lung conserve energy during one respiratory cycle, resulting in heat and lung tissue damage along each breath. In physical

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terms, the hysteresis area represents precisely this energy dissipated across the parenchyma and should bear some good correlation with VILI (12,13). For a single patient in which the respiratory system compliance (C_{RS}) is known, the total energy transfer is proportional to (driving pressure)^2 × C_{RS}. Therefore the total energy transferred is strongly determined by the driving pressure (defined as plateau pressure minus PEEP) delivered by the ventilator (12).

In the present study, Ladha *et al*. (14) analyzed the relationship between protective ventilation [defined as a PEEP ≥5 cmH_2O, tidal volume <10 mL/kg predicted body weight (PBW), and plateau pressure <30 cmH_2O] and major respiratory complications in a cohort of 69,265 patients who underwent non-cardiac surgical procedures. The authors found that protective ventilation was associated with decreased risk of complications [adjusted odds ratio (OR) =0.90; 95% confidence interval (CI), 0.82–0.98; *P*=0.013]. Also, a PEEP of 5 cmH_2O and median plateau pressures of 16 cmH_2O or less were associated with the lowest risk of postoperative respiratory complications. Finally, these results were similar in the propensity score matched cohort.

An interesting finding was an almost dose-response relationship between plateau pressure and major respiratory complications. This indicates that the current thresholds considered protective in critically ill patients with lung injury (<30 cmH_2O) may not be enough for patients with uninjured lungs. There are some concerns over the tidal volume reduction in patients with ARDS whose plateau pressure are already below 30 to 35 cmH_2O. In a study assessing potential reasons why physicians underuse lung-protective ventilation, although not explicitly documented as a reason for not using it, 82% of the patients who never received a protective strategy of ventilation had a plateau pressure ≤30 cmH_2O showing a preference for the plateau pressure as first aim for protective ventilation (15). However, in accordance with the findings from the study by Ladha *et al*. (14), a secondary analysis from the ARMA trial (16) suggests that there was a beneficial effect of tidal volume reduction, regardless of the level of plateau pressure (17). A target plateau pressure selected as low as possible to reduce driving pressure should be applied according to the present findings. In accordance, a recent study showed that decreases in driving pressure owing to changes in ventilator settings were strongly associated with increased survival in patients with ARDS (18).

An important aspect to be considered in studies in this field is the analysis of intervention bundles, in which the effects of single measure in the outcome is prone to criticism. Looking for the individual effects of plateau pressure, tidal volume and PEEP, the study employed separate regression models and found that only plateau pressures and PEEP were associated with the risk of respiratory complications. The rationale for using a bundle of low tidal volume and high level of PEEP with recruitment maneuvers can be that tidal volume reduction would induce atelectasis and higher levels of PEEP with recruitment maneuvers could stabilize the lungs during the respiratory cycle (19).

The use of higher tidal volumes was standard of care in the operating room for several years since use of tidal volumes per se prevents development of atelectasis, and as such improves oxygenation. Furthermore, relatively short use of higher tidal volumes was considered safe (20), despite the fact that animal as well as clinical studies showed that VILI can develop shortly after initiation of ventilation (21). Recently, several studies already strongly showed that tidal volume reduction in surgical patients is associated with decreased incidence of PPC (22-24).

Aiming to determine the impact of PEEP alone in surgical patients, the PROVHILO trial showed that during mechanical ventilation with low tidal volumes in patients undergoing open abdominal surgery, use of a high level of PEEP and recruitment maneuvers alone does not reduce the incidence of PPC (25). Thus, higher levels of PEEP (around 12 cmH_2O) with recruitment maneuvers more frequently results in hemodynamic instability and hypotension compared with low PEEP (around 2 cmH_2O) without recruitment maneuvers. These results were later confirmed in a large individual patient data meta-analysis including several randomized controlled trials in surgical patients, showing that low tidal volumes, but not PEEP, were associated with improved outcome in different types of surgery (26).

An alternative approach during general anesthesia is the so-called "intraoperative permissive atelectasis", when PEEP is kept relatively low and recruitment maneuvers are waived (19). This concept aims at reducing the static stress in lungs, which is closely related to the mean airway pressure, assuming that collapsed lung tissue is protected against injury from mechanical ventilation (19). Indeed, a recent study showed that a strategy using low tidal volume and minimal PEEP, resulting in a low driving pressure, is capable to protect the lung from VILI in animals model of ARDS, where the amount of atelectatic tissue is in fact much higher than those in uninjured lungs (27).

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The influence of outcomes used in the study with other relevant outcomes, including hospital length of stay and mortality still needs further studies. Composite endpoints as used in the present study are useful in that they provide an overall summary of effect, which may be readily appreciated by clinicians. When adequate, they enhance comprehension, study power, and precision, and these should lead to earlier identification of real improvements in care (28). However, composite outcome measures has some major limitations since the component variables can differ importantly in terms of severity and frequency, and differences in the frequency of component variables in a composite outcome may be masked (29).

In conclusion, the findings of the present study are one more brick in the wall showing the potential benefits of intraoperative protective mechanical ventilation. However, the impact of each parameter included in the bundle needs further assessment. According to available evidence and taking into account the present findings, mechanical ventilation of patients undergoing general surgery should include low tidal volume, low plateau pressure, and low driving pressure. However, higher levels of PEEP are still under debate and should be considered in selected cases.

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"Open the lung and keep it open": a homogeneously ventilated lung is a 'healthy lung'

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The acute respiratory distress syndrome (ARDS) has been a major cause of morbidity and mortality in the intensive care unit (ICU) for over four decades. What was thought to be a universally fatal form of double pneumonia was first identified in 1967 as a unique clinical entity and is now what we call ARDS. Ashbaugh *et al*. first identified ARDS as a unique disease triggered by a collection of pathologic abnormalities from initiating injuries such as sepsis, pneumonia, trauma or burns (1). In addition, this group demonstrated that ARDS mortality could be significantly reduced if positive end expiratory pressure (PEEP) was added to the ventilator strategy (1). Mortality secondary to ARDS was almost 70% from 1967–1979 and has been reduced progressively over the decades [60%: 1980–1989; 50%: 1990–1997] to the current mortality of ~40% [1998-2013] (2). Although we have significantly reduced ARDS mortality from when it was first identified, mortality has not been reduced any further over last 15 years (3).

Pharmacological treatments of ARDS have been largely unsuccessful (4). The most successful therapeutic strategies to date have been proning the patient (5) and low tidal volume (Vt) ventilation strategy (6). Increasing PEEP has not been shown to improve mortality below that of low Vt (7) except in subgroup analysis of the most severe ARDS cases (8). Thus, there is an urgent need to develop new ventilation strategies to reduce ARDS mortality. In 1992, Dr. Lachmann coined a phrase, "*Open the lung and keep it open*", to use as a lung protective strategy (9). The hypothesis behind this statement is that heterogeneous lung inflation, which is a hallmark of ARDS pathology, is a major cause of further lung damage during mechanical ventilation. The corollary to this hypothesis is that if you can open the lung and keep it open, the homogeneously ventilated lung would be protected from ventilator induced lung injury (VILI) and ARDS mortality would be reduced.

Kacmarek *et al*. recently published a pilot randomized controlled clinical trial testing the 'open the lung and keep it open' hypothesis on patients with established ARDS (10). This study compared the standard of care low Vt ventilation strategy (6) with an open lung approach (OLA). Using the OLA, the lung was first recruited and the level of PEEP necessary to keep the lung open following recruitment was individualized to each patient using a decremental PEEP trial. The combination of these two consecutive interventions is what separates the OLA from a simple lung recruitment maneuver using a set pressure over a period of time (i.e., airway pressure set at 40 cmH_2O and held for 40 seconds without PEEP adjustment). In addition, the OLA used in this study differed from studies in which PEEP was set without first recruiting the lung. Without an initial lung recruitment, even with identical PEEP levels, ventilation will be at a much lower end-expiratory lung volume, exacerbating lung heterogeneity (11). Another difference between this study and previous randomized controlled trials (12-14) is that patients were reevaluated 24 hours after ARDS diagnosis to ensure only patients with established ARDS were randomized. Thus, patients enrolled in this study had a more severe lung injury than in previous published trials (12-14). The study showed that the OLA improved oxygenation and reduced driving pressure but did not reduce mortality or ventilator-free days. However, their 60-day (28%) and ICU (25%) mortality in the OLA group was one

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of the lowest reported for patients with established ARDS. Although the study was initially powered for 600 patients it was terminated with 99 patients in the OLA groups and 101 patients in the ARDS net low Vt group for a number of logistical reasons. However, the promising results in the secondary endpoints support the need for a multicenter trial comparing OLA against the low Vt standard of care.

This is an important study since it supports our current understanding of the pulmonary pathophysiology associated with ARDS and the role played by mechanical ventilation in either preventing or exacerbating this initial lung injury. A recent review on the impact of mechanical ventilation during progressive acute lung injury shows that a physiologically based ventilation strategy can block all of the pathologic tetrad that are the hallmarks of ARDS (15). Multiple combinations of mechanical breath parameters, most often Vt and PEEP, in many animal models of ARDS have been shown to reduce pulmonary vascular permeability, pulmonary edema, preserve surfactant function and stabilize alveoli, minimizing strain-induced tissue damage known as atelectrauma (15). Thus, the physiologic foundation for protective mechanical ventilation is well established and all that is necessary is to identify the optimal combination of mechanical breath parameters (e.g., airway pressures, volumes, flows, rates and the duration that they are applied to the lung during both inspiration and expiration) that maximize lung tissue protection.

To this end, Gattinoni's group recently published two papers using an engineering analysis to determine the impact of the mechanical breath on the lung injury (16,17). They demonstrated that the applied stress, which for the lung is the Vt, impacts: (I) lung anatomy resulting in either collapse and heterogeneity or recruitment and homogeneous ventilation; (II) the energy load placed upon the lung and (III) dynamic strain (e.g., the change in lung size and shape in response to the applied stress) on lung tissue. Their studies showed that if the volumetric threshold (i.e., the limit of inspiratory capacity) was exceeded VILI occurred, secondary to stress rupture (pneumothorax). However, if the lower limit of inspiratory capacity was reached, but not exceeded, excessive dynamic strain (high Vt plus low PEEP) caused VILI, whereas a high static strain (low Vt plus high PEEP) did not (16). In addition, Protti *et al.* showed that PEEP was lung protective as long as it was associated with reduced Vt, increasing static strain but reducing dynamic strain (17).

Would the OLA be lung protective using this engineering analysis? The plateau pressures in the Kacmarek study (10) were less than 30 cmH_2O, suggesting that the inspiratory capacity was not exceeded and thus preventing VILI due to stress rupture. Also the PEEP was higher (static strain) and the Vt was lower (dynamic strain) on days 1 and 3, thus stabilizing the lung and minimizing dynamic strain, which was shown to be the major mechanism of VILI (16,17). Gattinoni's group also stressed that in ARDS the "inhomogeneity factor" with uneven distribution of volumes and pressures could induce local stress/strain relationships double that of the entire lung. Thus, recruiting the lung before application of an appropriate and personalized PEEP to keep the lung open would result in improved homogeneity, further protecting from VILI (10). The improvements in lung function using the OLA in the Kacmarek study make sense from a physiologic standpoint, supporting further work with this protective lung strategy.

From a physiologic standpoint if conventional mechanical ventilation (CMV) is used to ventilate patients with established ARDS, the OLA strategy should be optimal to, 'open the lung and keep it open'. However, an alternative strategy would be to, 'Never let the lung collapse'. Recent studies suggest that the preferred strategy in patients at high-risk would be to reduce the incidence of ARDS, using a preemptive mechanical ventilation strategy. This preemptive strategy would apply protective mechanical ventilation as soon as the patient is intubated, before the development of acute lung injury (18). With an ARDS mortality still at ~40%, with no decrease in over 15 years, reducing ARDS incidence is a very appealing approach. In addition to a preemptive low Vt strategy using CMV (18) others have shown reduced ARDS incidence in a high-fidelity, clinically applicable animal ARDS model (19) and a clinical statistical analysis (20) using preemptive airway pressure release ventilation (APRV).

In conclusion, based on our current knowledge of lung pathophysiology the OLA seems optimal for patients on CMV with established ARDS. Hopefully, improved preemptive ventilation strategies designed to reduce ARDS incidence may render the very difficult job of ventilating the ARDS patient obsolete, greatly reducing the morbidity and mortality of this serious medical problem.

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Footnote

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How to improve assessment of balance in baseline characteristics of clinical trial participants—example from PROSEVA trial data?

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Abstract: The randomization process is expected to balance assignment between the groups, independent to the participant and/or investigator, and as such avoids systematic error. However, it is recognized that groups assigned through the randomization process are not completely the same. Generally, a table with baseline characteristics is provided, where investigators report demographic and pertinent clinical variables based on the random group assignment and P values for the each variable in attempt to either support the balanced assignment or to indicate that the balance between groups was not ideal. The recently published PROSEVA trial showed more than 50% relative risk reduction of 28-day mortality among ARDS patients in the prone group compared to the supine group. In order to demonstrate a novel approach and exemplify how imbalance in baseline characteristics between groups could have potentially contributed to the large observed effect, we pooled pertinent baseline clinical variables from the trial in a meta-analysis-like manner. In addition to the quantification, we assigned the variable's "quality" of probable effect on the outcome as likely beneficial or harmful. After pooling pertinent dichotomous variables by the probability of their effect on the outcome, it appeared that approximately 37% (18% to 60%) of the observed PROSEVA trial effect could have been due to differences in baseline clinical characteristics. The main limitation of this approach is that all variables are assumed to have similar weights on the outcome. Interestingly, the weights of beneficial and harmful effects on the outcome were very similar. The proposed method of assessment of potential imbalance between the intervention groups assesses not only the magnitude of the difference, but rather the pooled probability of beneficial or harmful effect towards outcome, as well. As such, it could be useful as a secondary measure for the assessment of imbalance in the trials with the unexpectedly large observed effects.

Keywords: Randomization; balance; chance

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Introduction

Randomization, balance and chance

Randomization in research and evidence-based medicine represents the term for random assignment of patients in one of two (or more) intervention groups. The underlying idea is that the randomization process is able to balance assignment between two (or more) groups, independent to the participant and/or investigator, and as such will avoid systematic errors in the group assignment process. However, it is recognized that groups assigned through the randomization process are not completely the same; rather the expectation is that the groups are well balanced on known and unknown (confounding) factors. Thus, after properly done randomization, only remaining imbalance should be due to chance (1,2).

The investigators are usually aware of pertinent variables prior to designing the research study. As they would want to limit the effect of potentially confounding variables, they may use different randomization strategies. Some of these techniques are block randomization, sequence randomization, balance-tool based on the most pertinent clinical variables, etc. (1). Regardless of the strategy used to improve the randomization, the resulting expense lies

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Table 1 Patient characteristics extracted from PROSEVA trial (3)

Characteristic	Supine group (*n*=229) (%)	Prone group (*n*=237) (%)
Diabetes	39 (17.0)	50 (21.1)
Renal failure	12 (5.2)	10 (4.2)
Hepatic disease	16 (7.0)	15 (6.3)
Coronary artery disease	24 (10.5)	24 (10.1)
Cancer	30 (13.1)	24 (10.1)
COPD	29 (12.7)	23 (9.7)
Immunodeficiency	38 (16.6)	32 (13.5)
SAPS II	47±17*	45±15*
Sepsis	195 (85.2)	194 (82.2)
SOFA score	10.4±3.4*	9.6±3.2*
ARDS due to pneumonia	133 (58.1)	148 (62.4)
Body-mass index	29±7*	28±6*
Vasopressors	190 (83)	172 (72.6)
Neuromuscular blockers	186 (82.3)	212 (89.5)
Renal-replacement therapy	39 (17.1)	27 (11.4)
Glucocorticoids	101 (44.9)	91 (39.6)

*, data are shown as mean ± SD.

in the sample size requirement to enable the effective implementation of the chosen randomization strategy. Even when sample size is large, it is usually not feasible to balance on all pertinent variables through the randomization strategy. In studies with smaller targeted sample sizes it is not possible to effectively use randomization balancing strategies. Also, one needs to accept the presence of inapparent pertinent factors for which there is no effective way of balancing. What remains then are the effects of chance, which still should be considered and at times more closely evaluated.

Current state

Univariate comparisons between intervention groups

Most peer reviewed publications of clinical trials include a table with general or baseline characteristics marked as *Table 1*. In this table, investigators report demographic and pertinent clinical variables based on the random group assignment. This table allows readers to assess for (im) balance between groups' characteristics, potential for selection bias, as well as applicability of the study to their practice (2). Frequently, authors report P values for the each variable in *Table 1* in attempt to either support the balanced assignment in the case of non-significant P value (usually ≥0.05), or to indicate that the balance between groups was not ideal, if P value was significant (usually <0.05). The P values for each individual characteristic (variable) are calculated by univariate analysis by using Chi-Square or Fisher's exact test, as applicable. These tests are able to measure and signify the difference among expected and observed values. However, in these cases, there is usually an oversight of the basic statistical principle of hypothesis testing. Although the investigators expect the differences to be insignificant, there is no formal preset hypothesis accompanied with the power analysis. The end result is that the *Table 1* with P values as measures of "significance" frequently distracts the readers from carefully analyzing balance in presented variables. More importantly, the balance on reported variables is only assessed by the univariate method. However, pertinent demographic and clinical variables are not completely independent one from another; therefore presumed balance between groups in individual variables does not necessarily equals the overall balance between intervention groups on all pertinent clinical variables.

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A different perspective

How to measure the differences in baseline characteristics between groups?

In order to better illustrate above mentioned issues, we will use the example of the recently published, "practice-changing", PROSEVA trial (3). This was a randomized controlled trial of 16-hour prone-positioning sessions versus supine position among adults with severe acute respiratory distress syndrome (ARDS) in 26 intensive care units (ICU) in France and 1 ICU in Spain. The study showed more than 50% relative risk reduction of 28-day mortality among patients in the intervention group compared to the supine group (16% *vs.* 32.8%; HR =0.39; 95% CI, 0.25–0.63; $P<0.001$). This was reported in the accompanying *New England Journal of Medicine* editorial as "Virtually unprecedented in modern medicine" (4). Although our intent is not to criticize this study or explain other potential underlying reasons for the large observed mortality effect, we need to mention the fact that this study was preceded by many studies on the same topic and none of the previous ones showed significant effect on the mortality. Two meta-analyses (5,6) published since the PROSEVA trial, suggest overall benefit of probing on mortality only after the inclusion of the PROSEVA trial results. The example that we will use from this study published in *New England Journal of Medicine* in 2013, is the depicted as *Table 1* (3).

Authors reported no significant differences between the groups in any of the baseline characteristics listed, with the exception of the Sepsis-related Organ Failure Assessment (SOFA) score, the use of vasopressors and the use of neuromuscular blockers. However, if one carefully analyzes the distribution of pertinent variables between two groups in the *Table 1*, it could be noted that in almost every single variable the balance is in "slight favor" of the intervention group. Diabetes as a coexisting condition was present in 21% and 17% in the prone versus supine group. Diabetes has been previously shown to be protective factor in ARDS development (7), and it was present more frequently in the prone group. There was more ARDS due to pneumonia in the prone group and it has been shown previously that the mortality of ARDS due to pneumonia (localized infection, direct ARDS) is lower than due to sepsis (systemic infection, indirect ARDS). On the contrary, there was more renal failure, hepatic disease, coronary artery disease, cancer, COPD, sepsis and immunodeficiency in the supine group, compared to the prone group. Although each of these variables individually was not deemed to be "significant", the (not so) obvious impression is that the supine group was not only sicker than the prone group, but also with more known risk factors for ARDS. Therefore, it is suggested that there was an imbalance in baseline harmful and protective risk factors for ARDS between groups. This was in a way confirmed by significant difference in severity of illness, SOFA score, between the groups. However, another severity of illness score, SAPS II, was not deemed to be significantly different, although it was higher in the supine compared to the prone group. Moreover, the patients in supine group received significantly more vasopressors and renal replacement therapy than those in the prone group. On the contrary, they received less neuromuscular blockers, which have been recently shown to improve mortality of ARDS patients by minimizing the ventilator-induced lung injury (VILI) (8).

How did the investigators address this imbalance between groups? After acknowledging the significant between-group differences by univariate P values only in SOFA scores, the use of vasopressors and the use of neuromuscular blockers, they adjusted for these variables in the Cox proportional hazards regression model of mortality. The question is whether this was sufficient. We again emphasize here limitations of separate, univariate analyses of highly correlated variables to assess their "significance" with the outcome. Although ICU severity of illness scores were shown to be helpful in predicting mortality based on the admission variables, lumping of pertinent variables into the composite score variable and subsequent adjustment might not be ideal. This is very similar to the issue of using composite outcomes instead of the individual ones from the evidence-based medicine perspective. More importantly, the general ICU severity scores do not encompass all potentially pertinent variables as could be seen in the PROSEVA trial example, and they are not specific for ARDS or any other disease.

So, how can we then improve the assessment for imbalance in variables reported in *Table 1*? In order to thoroughly assess the (im) balance, all pertinent reported variables should be taken into account. There are several potential ways to address this. One way would be to include and adjust for all the variables in the multivariate model for the primary outcome regardless of the univariate P values. This method may not be practical in the trials where sample size does not allow inclusion of large number of variables (10:1 general rule). Another proposed method could be to pool the variables from *Table 1* to assess their balance

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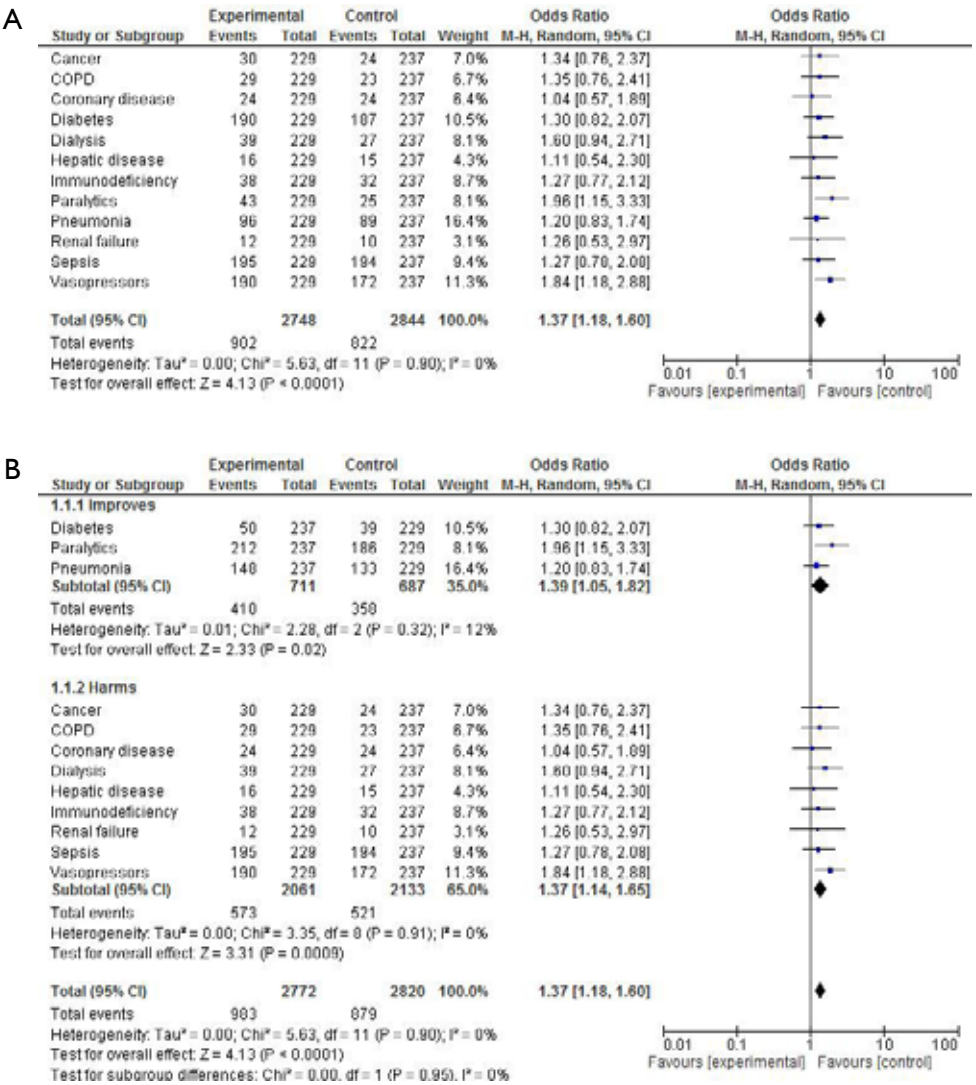

Figure 1 After pooling pertinent dichotomous variables by the probability of their effect (protective or harmful) on the outcome, in the random-effect model, it appears that approximately 37% (18–60%) of the observed PROSEVA trial effect could have been due to differences in baseline clinical characteristics. (A) All variables are shown together as a single group; (B) the variables are split in two subgroups based on their proposed protective or harmful effects.

relative to the outcome of interest. This could be done by pooling the pertinent reported variables in a meta-analysis-like manner. However, not only the "quantity" of the difference matters. It is important to split the variables by the "quality" of their known effect on the outcome. Based on the existing knowledge and the evidence in literature, the variables should be grouped into two subgroups; one with variables with likely beneficial (protective) effect and another subgroup with variables with likely harmful effect on the outcome. For the overall pooling of both subgroups, the ordering of experimental and control groups could be reversed for easier graphical interpretation in the forest plot. Above are the forest plot examples of pooled variables from PROSEVA trial, where we used random effect model and odds ratio (OR) estimate with 95% confidence intervals (*Figure 1*).

It can be seen from the forest plot examples above (*Figure 1A*,*B*) that by pooling all pertinent dichotomous variables with established direction of effect (protective or harmful) on the outcome from *Table 1*, one can appreciate

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Table 2 Severity of illness score differences

Variables	Supine (mean ± SD)	Prone (mean ± SD)	Mean difference	Standardized mean difference (SMD)*
SAPS II	47.0±17.0	45.0±15	2.00 [-0.91, 4.91]	0.125
SOFA	10.4±3.4	9.6±3.2	0.80 [0.20, 1.40]	0.242

*, overall SMD =0.184.

better the difference or imbalance of the two intervention groups. The random effect model estimated the pooled difference between the groups' baseline characteristics relative to their proposed effect towards primary outcome to be 37% higher in the control (supine) group (OR =1.37; 95% CI, 1.18–1.60; $P<0.0001$). Pooling of continuous variables, SAPS II and SOFA scores (*Table 2*), suggests that the standardized mean difference in these severity of illness scores between supine and prone groups was 0.184. Of note, the estimated effect of the SOFA score alone in the Cox proportional hazards regression model of mortality as a primary outcome in the trial was 19.4% per unit of score at inclusion (OR =1.194; 95% CI, 1.11–1.29; $P<0.001$). Since the observed difference in SOFA scores between two groups in *Table 1* was 0.8 units (10.4 *vs.* 9.6), observed overall magnitude effect of SOFA score for the primary outcome was 0.155 (0.194×0.8), which is less than the observed between-the-group difference in two combined scores of severity (*Table 2*). More than half (~20%) of the overall proposed imbalance (37%) as estimated by the novel approach from *Figure 1*, remains unaccounted for by using only adjustments by severity of illness scores.

We obviously do not consider this method to be without the flaws. The main limitation is that all the variables are assumed to have similar weight on the outcome, which is certainly distant from optimal. However, despite this limitation, this method is more formal in assessing the potential imbalance between intervention groups than the current method, because it relies not only of the magnitude of the difference, but rather on the proposed direction of the effect towards outcome (quality), as well. It is novel and could be further improved to report even more accurately on balance in baseline characteristics of the intervention groups. We think that correlation and/or dependance of pertinent baseline variables can't be ignored by choosing only the significant variables as indicated by univariate analyses. Also, by using composite estimates, as shown above with the examples of SOFA and SAPS II scores, the between-group differences could be substantially underestimated.

Other methods could prove to be more feasible, like perhaps one where the individual group's expected and observed values from 2×2 tables for all pertinent variables can be pooled and then compared to another group by Chi-square test. However, the direction of the estimated effect on outcome of interest is of crucial importance in order to correctly estimate proper balance. We favor the first example over the second one because of easier visual interpretation with the forest plot.

Conclusions

The proposed method of assessment of potential imbalance between the intervention groups assesses not only the magnitude of the difference, but rather the pooled probability of beneficial or harmful effect towards outcome, as well. As such, it could be useful as a secondary measure for the assessment of imbalance in the trials with the unexpectedly large observed effects.

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Footnote

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Quantification of lung recruitment by respiratory mechanics and CT imaging: what are the clinical implications?

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Provenance: This is a Guest Commentary Commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).

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Acute respiratory distress syndrome (ARDS) is characterized by increased elastance of the lung and respiratory system (1). Depending on the precipitating factor, pulmonary *vs.* extrapulmonary, the distribution of pathologic findings and altered respiratory mechanics in the lung is heterogeneous (2). Portions of the lung can be collapsed and/or fluid-filled while others are well-aerated. In order to facilitate gas exchange, recruitment maneuvers are sometimes employed in patients with ARDS (3). These can be performed with a constant high pressure inspiratory hold for 30–40 seconds (4,5) or via stepwise recruitment by increasing the positive end-expiratory pressure (PEEP) (6), typically followed by application of PEEP at a higher level than the previous baseline to maintain aeration of the recruited lung units (7). Recruitment maneuvers have been proposed as useful tools in managing patients with ARDS in order to add previously non-participatory lung units to gas exchange as well as to assess disease severity. The potential effectiveness of recruitment maneuvers in incorporating previously collapsed lung units into gas exchange or in improving the distension of previously poorly aerated pulmonary units differs from patient to patient consequent to the variability in etiology of the lung injury and the heterogeneity of lung parenchyma (8).

A recent study by Chiumello and colleagues compared computed tomographic (CT) to respiratory mechanics methodologies for the measurement of the effectiveness of lung recruitment in ARDS (9). For the CT method, CT scans of the lungs at two levels of inflation were used to assess the effectiveness of increased PEEP for recruitment of new lung units to gas exchange (8). For this method, pulmonary voxels are classified into groups based on relative density as measured by CT Hounsfield units (HU). By established convention, regions with HU of >–100 are designated as having no aeration, –100 to –500 poorly aerated, –500 to –900 good aeration, and –900 to –1,000 as over-distended. Comparing the number of voxels in each group in CT scans performed at 5 cmH_2O PEEP and 15 cmH_2O PEEP established recruitment as the change in mass of non-ventilated lung between the CT scans.

By contrast, respiratory mechanics methods for determining recruitment measure the change in total lung volume of a single breath at different levels of PEEP compared with the anticipated change in volume if compliance were unchanged. One method (termed the EELV-Cst, RS method by Chiumello *et al.*) measures the static compliance of the respiratory system for one breath at 5 cmH_2O PEEP and calculates the anticipated lung volume at 15 cmH_2O PEEP if compliance were stable. The expected increase is compared with measured end-expiratory lung volume by helium dilution at 15 and 5 cmH_2O PEEP. The lung volume measured at PEEP 15 cmH_2O in excess of what was predicted from compliance measurement is attributed to recruitment (10). A related method of slow-flow pressure-volume curves generated at PEEP 5 and 15 cmH_2O (termed the P-Vrs curve method by Chiumello *et al.*) similarly calculates recruitment in volume of gas as the measured volume at PEEP 15 cmH_2O compared with the volume anticipated at PEEP 15 cmH_2O when initiating the breath from PEEP 5 cmH_2O (10,11).

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As should be expected, the two assessments of recruitment based on respiratory mechanics, both of which premise pulmonary recruitment on the change in static compliance of the lung, yielded highly correlated results, though the absolute measured gas recruitment differed between the two techniques. The CT scan method, however, yielded levels of tissue recruitment that bore no relation to the gas recruitment estimated using the two respiratory mechanics methods.

Closer examination of the measured variables makes this the anticipated result. The measured gas recruitment from both respiratory mechanics methods is spread across the entirety of the lungs: the relative portion applied to changing distension of pulmonary units that were aerated at the lower PEEP *vs.* to the filling of previously non-aerated pulmonary units cannot be differentiated by respiratory mechanics. As a result, there is a positive correlation between well-inflated tissue at baseline and absolute gas recruitment measured by the respiratory mechanics methods (0.85 mL recruitment per gram of well-inflated tissue at PEEP 5 cmH_2O, R^2 =0.25, P=0.02). In contrast, the CT method specifically quantitates the shifting of previously non-aerated lung (HU >–100) to aerated lung (HU –1,000 to –100). As one would expect, the more non-aerated lung there is at baseline, the more recruitment occurs with increased PEEP, (0.12 mL recruitment per gram of not inflated tissue at PEEP 5 cmH_2O, R^2 =0.44, P<0.001). In other words, increased PEEP can only recruit non-aerated pulmonary units if there are non-aerated pulmonary units at baseline.

In sum, Chiumello *et al.* find that lung recruitment measured in ARDS via respiratory mechanics is quite distinct from recruitment measured by CT scan. The respiratory mechanics methods quantitate increased aeration of already open pulmonary units on top of the addition of previously non-participatory, collapsed pulmonary units to gas exchange, whereas the CT scan method measures only the addition of previously collapsed pulmonary units to gas exchange.

CT scan has the added benefit of quantitating how much lung parenchyma shifts from "under-inflated" or "well-inflated" as defined by HU to "over-inflated." On average, increasing PEEP from 5 to 15 cmH_2O yielded a decrease in non-inflated tissue from 656 grams (44%) to 579 grams (37%) (P<0.001), which was partially offset by an increase in over-inflated lung from 4 grams (0.3%) to 10 grams (0.7%) (P=0.288). The increase in over-inflated lung when quantitated by gas volume was statistically significant, but the absolute numbers were not reported. Importantly, over-distension as measured by CT was at end-expiration—over-distension at end-inspiration is probably more relevant for ventilator-induced lung injury and was not measured.

It is notable that the recruitment as quantified by either methodology correlates poorly with indices of gas exchange. Plotting delta PaO_2, delta PaO_2/FiO_2, delta $PaCO_2$, and delta shunt *vs.* recruitment from each method yielded only two statistically significant correlations (CT-measured tissue recruitment correlated with delta PaO_2 and with delta shunt but with correlation coefficients of just 0.26 and 0.19, respectively). Thus, as the investigators duly note, improved oxygenation after recruitment with increased PEEP cannot be proportionally attributed to increased lung volume alone.

While Chiumello *et al.* nicely differentiate the features of recruitment by CT compared to respiratory mechanics, they comment little on the significance for clinical practice because at present these remain research tools. As the investigators point out, CT scans are unappealing for routine use since they are laborious, require radiation exposure, and require potentially dangerous transport. Respiratory mechanics are theoretically more attractive because of their potential for measurement at bedside, though they require heavy sedation and frequently neuromuscular blockade to perform reliably (10,11). That they measure different components of pulmonary recruitment ignores the fact that the benefit of recruitment maneuvers in routine clinical practice is unproven, and the clinical utility of quantitated measures of recruitment is unknown.

To date, studies of recruitment maneuvers with hard patient-centered outcomes such as survival have largely incorporated recruitment maneuvers as part of a package of interventions for lung protection; benefits of their isolated use are unclear (4,6,12-14). While the opening of collapsed pulmonary units by recruitment maneuvers seems intuitively beneficial, it may be accompanied by harmful over-distension of already well-aerated lung, and determining the balance of benefit *vs.* harm is challenging. Indeed, critical care research is rife with examples where a logical physiological endpoint did not equate to better patient-centered outcomes. Consider that in the now classic ARDS Network trial of lower tidal volume ventilation, the higher tidal volume group had better oxygenation yet had an 8.8% absolute higher mortality rate (15). At present, the best evidence for lung protective ventilation in ARDS incorporates relatively low tidal volume ventilation with

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minimized plateau pressures. The balance of the risk of over-distension of some lung units to the benefit of keeping open and preventing atelectotrauma in others is uncertain and probably varies for the individual patient and their relative at-risk pulmonary units, though there is growing belief that higher PEEP is beneficial in severe ARDS (16). Some large trials which include the use of recruitment maneuvers are ongoing and will potentially better inform the critical care community on the utility of recruitment maneuvers in the future (NCT01667146, NCT01374022).

To the practicing critical care physician, there are two useful take home messages from Chiumello *et al.*'s investigation: (I) changes in respiratory exchange measures (i.e., PaO_2, $PaCO_2$, and shunt) are minimally associated with quantitated recruitment either by CT or respiratory mechanics; and (II) measurement of gas recruitment by respiratory mechanics in ARDS does not imply that previously non-aerated lung units were added to gas exchange. The investigators posited that "[r]ecruitability may be important in clinical practice for assessing the severity of ARDS, planning recruitment maneuvers and setting adequate PEEP levels during mechanical ventilation", but the current study does not yet allow us to define the clinical role of assessing "recruitability" (9). Thus, there is no compelling reason as of yet for a clinician to attempt to quantitate lung "recruitability" as part of clinical care in ARDS. As for whether recruitment maneuvers should be routinely applied in management of ARDS: the answer is not yet known.

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Footnote

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Fever: suppress or let it ride?

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Abstract: While our ability to detect and manage fever has evolved since its conceptualization in the 5th century BC, controversy remains over the best evidence-based practices regarding if and when to treat this physiologic derangement in the critically ill. There are two basic fields of thought: (I) fever should be suppressed because its metabolic costs outweigh its potential physiologic benefit in an already stressed host; *vs.* (II) fever is a protective adaptive response that should be allowed to run its course under most circumstances. The latter approach, sometime referred to as the "let it ride" philosophy, has been supported by several recent randomized controlled trials like that of Young *et al.* [2015], which are challenging earlier observational studies and may be pushing the pendulum away from the Pavlovian treatment response.

Keywords: Critical care; acetaminophen; infection; ICU; febrile

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Historical perspectives and progress

The concept of "fever" has been a major focus of medicine for centuries, and while our ability to detect and manage fever has evolved, controversy remains over the best practices with respect to the treatment of this physiologic derangement. Hippocrates, in the 5th century BC, was perhaps one of the first to understand and characterize fever as part of the immune response (1). Sydenham described fever as "*nature's engine which she brings into the field to remove her enemy*" (2). Several giants in medicine continued attempts to characterize the role of fever in infection over the next twenty centuries such as Galen of Pergamon and Girolamo Fracastoro, but were limited in that their understanding considered fever as a disease in itself rather than a sign of other disease (3). Further impeding the understanding and study of fever was the lack of a reliable and valid measurement tool, which was not widely applied until the 19th century when Karl Wunderlich instituted the use of thermometers and temperature cards to monitor changes in patients over time, therefore incorporating this vital sign into the standard diagnostic algorithm (3).

The next challenge in the characterization of fever was the creation of a uniform definition. Currently, this delineation is still arbitrary and dependent on the purpose for which it is defined. In general, fever is defined as an elevated body temperature above normal variation due to an altered hypothalamic set point. A joint task force from the American College of Critical Care Medicine and the Infectious Diseases Society of America defines fever as a body temperature of 38.3 ℃ (101 ℉) or higher, which is generally accepted as fever for patients in the ICU setting (4).

While it took centuries to reach somewhat of a consensus regarding the characterization and definition of fever, unanimity concerning when and if to treat it in critical care patients is still in its infancy. Complicating this matter is both the heterogeneous etiology of fever as well as practice dogma. While 70% of ICU patients manifest fever, only about 53% are of infectious etiology (5). Despite its source, practitioners often seem to possess an ingrained philosophic opposition towards fever, prompting a knee-jerk response to treat that is not supported by high-level evidence in the ICU population.

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Suppress it

In general, two critical assumptions form the basis of the argument for treating fevers, neither of which have been experimentally validated: (I) fever is noxious, and (II) suppression of fever will reduce its noxious effect (6,7). One condition justifying treatment consideration is when a fever's metabolic cost exceeds its physiologic benefit, but this again, is challenging to quantify (6,8). The only clinical condition with abundant evidence to support aggressive antipyretic treatment is in acute brain injury (9-11). Even the management of febrile seizures in the pediatric population has moved away from antipyretic use as prophylaxis since fever reducing drugs do not reduce seizure recurrence (12,13). Fever reduction via cooling in the ICU setting has been documented in a randomized controlled trial to be of benefit in patients with septic shock leading to a reduction in vasopressor use and mortality (14). Most of the other studies supporting the association of fever with poorer outcomes have been observational in nature (15). In theory, these critically ill patients and those faced with additional physiologic stress may benefit from fever reduction (8), but the evidence on both sides of the argument appears to be mostly equivocal.

Let it ride

Those in the "let it ride" camp advocate that fever is a protective mechanism with benefits ranging from enhancing immune-cell function to promoting antimicrobial activity (16,17). In the past decade several studies have supported this hypothesis. A randomized control trial published by our institution in 2005 sought to evaluate the impact of antipyretic therapy on outcomes in critically ill patients (18). Patients were randomized to an aggressive treatment group, consisting of acetaminophen 650 mg every 6 hours for fever >38.5 ℃ with addition of a cooling blanket for temperature of >39.5 ℃, or a permissive group where treatment was initiated at a temperature of >40 ℃ with acetaminophen and cooling blankets. The study had to be terminated at the interim analysis as there were seven deaths in the aggressive group and only one death in the permissive group. Another randomized controlled trial in critically ill patients without neurotrauma or severe hypoxia also failed to support the treatment of fever showing no significant differences in fever recurrence, infection, antibiotic therapy, ICU and hospital length of stay, or mortality between those receiving external cooling for temperature ≥38.5 ℃ *vs.* no antipyretic treatment (19).

New evidence

Despite this evidence, treatment of fever is common in the ICU setting and likely related to standard dogma rather than evidence-based practice. In this prospective controlled trial by Young *et al.* published in the *NEJM* on December 3, 2015, 700 ICU patients with fever of known or suspected infectious etiology were randomized to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death (20). The patients in the treatment group did have a statistically, but likely not clinically, relevant lower mean daily average temperature (absolute difference −0.28 ℃, $P<0.001$). Sustained resolution of fever was also significantly higher in the treatment versus placebo group (22.8% *vs.* 16.9%, $P=0.05$). The main outcome was ICU-free days until day 28, which was not shown to be decreased in the treatment arm. Secondary outcomes, including 28 and 90-day mortality and ICU and hospital length of stay, were also not significantly different between groups. However, acetaminophen was associated with a shorter ICU stay than placebo among survivors and a longer stay in non-survivors. In terms of adverse events, there was no difference between groups in discontinuation of the drug due to liver dysfunction, and one patient in the placebo group suffered from markedly elevated temperature associated with death. It should be noted that the study population was predominantly non-surgical and that the treatment period was relatively short. More and more high-level randomized controlled trials are supporting the "let it ride" philosophy compared to the original prospective observational studies, which seem to support the opposite.

To treat or not to treat?

Is fever good or bad? Scientifically, we just do not know. However, if we take the evolutionary perspective, then blunting of the adaptive febrile response must be maladaptive. Fever is estimated to be more than 4 million years old and has been documented in the phyla Vertebrata, Arthropoda, and Annelida (7). Despite its long history of study, the exact mechanism of fever and its potentially protective effect is not fully delineated. One

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could hypothesize that treatment of fever compromises immune competence and renders patients more susceptible to infection. Take, for example, the classic experiment by Kluger *et al*. in 1981 (21,22). Here, Kluger *et al*. infected cold-blooded iguanas with bacteria. He gave them the opportunity to seek heat via sunlamps and all but one sought the warmth to raise their temperature. The one who did not was the only one who died. Next, he injected the iguanas with bacteria and gave them antipyretics. The iguanas that were able to mount a fever despite the antipyretic were the only ones that survived. This simplistic experiment, in addition to the biologic plausibility for the beneficial effects of fever, now supported by several key randomized controlled trials, suggests maybe the pendulum is due to swing back to a more permissive approach to fever.

While clinicians will likely continue to argue the validity of the proposed adaptive or maladaptive mechanisms of fever, recent studies such as the one by Young *et al*. should support reconsideration of the Pavlovian treatment response to elevated temperature in the critical care setting.

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Footnote

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Acetaminophen in critically ill patients, a therapy in search for big data analytics

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Young *et al.* presented a study of randomly assigned ICU patients (*n*=700), with fever (body temperature ≥38 ℃) and known or suspected infection to receive either 1 g of intravenous acetaminophen or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. The primary outcome was ICU-free days (days alive and free from the need for intensive care) from randomization to day 28. Early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days.

Concluding that early administration of acetaminophen does not affect the number of ICU-free days should be viewed in perspective of the study limitations. The authors used a temperature ≥38 ℃ to classify patients with fever (1). Taking into consideration the variance related to the anatomical location of the measurement, the diurnal temperature cycle, and the technology applied, using 38 ℃ instead of 38.3 ℃ might be of limited importance. However, no mention is made of this choice of threshold or its possible consequences. Study inclusion too deserves further scrutiny. Out of a total of 3,601 patients meeting inclusion criteria only 700 underwent randomization spread over 23 adult ICU's, though 1,053 eligible patients were not enrolled. Protocol violations, in this case open-label acetaminophen administration, were high in both the acetaminophen (30%) and placebo (29%) groups, predominantly in the latter phases of ICU treatment. Use of the study drug before randomisation or after discharge from ICU was not reported. Finally, study drug administration was short compared to length of ICU stay. These combined weaknesses undermine the findings of the study, watering down any possible differences between the two study groups. In view of these shortcomings it is understandable that no considerations have been made on a potential extrapolation of the use of oral acetaminophen in this patient population (2).

However, the question posed by this study is clinically relevant. It might appear reasonable to give acetaminophen to patients in whom the fever is causing distress but it is similarly reasonable to withhold it in patients who are not distressed. In suspected infection, mild to moderate fever may prove beneficial in fighting infection. Evidence proving benefit of treatment for mild to moderate fever is scarce, apart from in cardiogenic shock, extreme hypoxemia or acute brain injury (3). A study *in vitro* demonstrated that differentiation of $CD8^+$ T cells into effector cells is enhanced by physiological range hyperthermia, with optimal enhancement at 39.5 ℃ (4). Similar advantageous effects were demonstrated in macrophages which play a pivotal role in innate immunity, enhancing early immunological responses to infection. In a murine model, LPS was utilized to model an aseptic endotoxin-induced inflammatory response studying the effects of elevation in body temperature to fever range. Fever enhanced and prolonged subsequent responsiveness of macrophages to the endotoxin challenge (5).

The methodology and its apparent shortcomings limit the value of findings and demand further discussion. Undoubtedly much time and effort has been invested and the abovementioned, often unavoidable, shortcomings must frustrate those who designed the study, begging the

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question: what alternatives are there? (6). Predictive analytics could stimulate the transformation of reactive medicine (fever means acetaminophen treatment) towards more predictive, preventive and personalized medicine (PPPM) , ultimately affecting both cost and quality of care (7-9). However, high-dimensionality and high-complexity of the data involved, prevents data-driven methods from easy translation into clinically relevant models. Additionally, the application of cutting edge predictive methods and data manipulation require substantial programming skills, limiting its direct exploitation by medical domain experts. The existing, large databases providing inclusion of more patients (e.g., MIMIC-III database) (10) and the use of open, visual environments, suited to be applied by the medical community could stimulate the meaningful use of data from critical care patients. This could minimize the gap between potential and actual data usage (11).

In conclusion, Young *et al.* have reopened an important debate questioning the routine use of acetaminophen for fever control in the setting of infection. Studying the use of a drug which is so ingrained in clinical practice will always be arduous. Novel predictive analytics in large databases may provide a timely new tool for further study. Though it seems that this study has too many shortcomings to be able to change clinical practice once and for all, the clinician is right to question the use of acetaminophen in mild and moderate fever in patients in no apparent distress.

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Footnote

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Acetaminophen for febrile patients with suspected infection: potential benefit and further directions

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Fever, increased body temperature, is a physiological expression of the host's response to an infective (1) or non-infective pathology (2-6). Non-infective fever is common in critically ill patients, which includes ones related with post-surgical reaction, acute myocardial infarction, cerebral infarction, cerebral hemorrhage, acute pancreatitis, malignant tumor, post-transfusion reaction, transplant rejection and drug fever. Fever is also common in infective patients. In multicenter observational study, among the patients who developed body temperature equal or more than 38.5 ℃, approximately 63% of patients were diagnosed as sepsis (7).

Fever may have detrimental effects such as increasing the oxygen consumption and worsen the neurological outcomes (8-10). Thus, antipyretic treatments are frequently administered in critically ill patients. Among septic patients, at least one antipyretic therapy was prescribed in one-third of patients who developed body temperature between 38.5–39.4 ℃, and more than half of patients that body temperature equal or more than 39.5 ℃ (7). However, high body temperature could be an optimal host response against infectious disease. Fever may result in reduced bacterial growth, promotion of the synthesis of antibodies, and activation of T cells, neutrophils and macrophages (11-13). In this regards, the antipyretics could be either friends or foes in patients with infection. It is unfortunate that the impact of antipyretics in infective patients has been unclear and there are no recommendations for body temperature control for febrile patients with infection (1,14).

One randomized controlled study in 1997, ibuprofen administration (10 mg per kilogram of body weight) significantly decreases fever and oxygen consumption in septic patients. This study did not show any benefit of ibuprofen on the patients' centered outcome including the incidence of the acute respiratory distress syndrome and mortality (15) (*Table 1*). In this study, 44% of the patients in the placebo arm were received acetaminophen administration and 22% of those in the ibuprofen arm. In this regards, the impact of ibuprofen as an antipyretics on the outcomes in septic patients might not be able to determine in this study (18). However, one may consider that this study might show that the reduction of body temperature to normothermic range (36.5–37.0 ℃) may be safe in septic patients.

Another randomized controlled study was conducted to assess the effect of external cooling in 200 febrile adult patients with septic shock who were sedated, required mechanical ventilation and received vasopressor. External cooling for 48 hours was reduced body temperature in the normothermic range (36.5–37.0 ℃). External cooling significantly reduced the vasopressor requirement and mortality at 14 days after randomization (16) (*Table 1*). This trial also showed that the acquired infections for 14 days was tended to be increase in cooling arm in compared with non-cooling arm (32.6/1,000 *vs*. 23.8/1,000 ICU days, P=0.25). Then, the mortality benefit observed at Day 14th did not remain at ICU or hospital discharge. The major concerns to apply external cooling in febrile patients were patient's discomfort and potential shivering. To prevent shivering, sedative drugs may be required. We should note that they choose the septic patients who were sedated and

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Table 1 Large randomised controlled trials to assess the antipyretics in febrile critically ill adults (number of patients in one arm equal or more than 100)

First author, year	Patients	Summary of study
Bernard *et al*. 1997 (15)	455 patients with sepsis	Antipyretics Intravenous ibuprofen administration (10 mg/kg) every 6 hourly for eight doses (48 hours) Body temperature Ibuprofen administration significantly reduced body temperature Body temperature at 48 hours after randomization was 36.9 ℃ in ibuprofen group Outcomes Ibuprofen did not change the 30 day mortality Ibuprofen did not alter the incidence shock and ARDS Ibuprofen significantly decreased heart rate, oxygen consumption, serum lactate levels Second infection Second episodes of sepsis occurred in 8.2% in ibuprofen group and 11.1% in placebo group Complications Ibuprofen did not alter the renal function, the incidence of hemodialysis requirement, transfusion requirement and gastrointestinal bleeding
Schortgen *et al.* 2012 (16)	200 patients with septic shock	Antipyretics External cooling for 48 hours to maintain body temperature between 36.5 and 37 ℃ Body temperature External cooling significantly reduced body temperature Body temperature at 48 hours after randomization was 36.8 ℃ in cooling group Outcomes The percentage of patients with a 50% vasopressor dose decrease versus baseline was significantly higher in the cooling group at 12 hours after randomization. This difference was not remains at 48 hours Day-14 mortality was significantly lower in the cooling group. This difference was not remained at ICU and hospital discharge Second infection The density of acquired infections at Day 14 was 32.6/1,000 ICU days in cooling group and 23.8/1,000 ICU days in non-cooling group (P=0.25) Complications No patient developed hypothermia. In the cooling group, two patients with cooling stopped because of shivering
Young *et al.* 2015 (17)	700 patients with fever and known or suspected infection	Antipyretics 1 g of intravenous acetaminophen every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death Body temperature Administration of acetaminophen significantly reduced body temperature Mean body temperature at Day 2 was 36.9 ℃ in acetaminophen group Outcomes There was no significant between-group difference in number of ICU-free days, 28-day mortality, 90-day mortality, or survival time to Day 90 Second infection Not reported Complications The incidence of liver dysfunction led to discontinuation of the study drug was not significantly differed between two groups There was a patient with markedly elevated body temperature associated with death in one patient in control group

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required mechanical ventilation.

Although above RCTs reported the lack of adverse effect or potential benefit of lowering body temperature using ibuprofen and external cooling in septic patients, those of two may not be a major antipyretic used in critically ill patients. The administration of acetaminophen would be common antipyretic in critically ill patients. One retrospective study including 15,818 ICU patients had shown that 64% of study patients received at least 1 g of acetaminophen. And the administration of acetaminophen was independently associated with decreased mortality both in surgical and medical patients (19). However, antipyretic therapy may vary among countries. In a prospective observational study conducted in Korea and Japan including 1,425 critically ill patients had shown that acetaminophen was used in 10.4% of patients (7) and the administration of acetaminophen was independently associated with increased mortality in septic patients. This controversy seen in these two observational studies suggests that there may be major confounders on the association between the acetaminophen administration and mortality. Thus, the randomised controlled trial to assess the impact of acetaminophen in patients with infection was definitely necessary.

Acetaminophen for fever in critically ill patients with suspected infection

Recently, "the Permissive Hyperthermia through Avoidance of Acetaminophen in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial" was published in *New England Journal of Medicine* (17) (*Table 1*). They included 700 patients with ≥38 ℃ of body temperature and known or suspected infection. Patients were randomly assigned to receive either 1 g of intravenous acetaminophen or placebo every 6 hours. The study drugs were stopped when body temperature was less than 37.5 ℃ for last 24 hours, antimicrobial treatment was stopped or patients were discharged from ICU discharge. They allowed using the physical cooling at body temperature equal or more than 39.5 ℃. They also permit to use the open-label acetaminophen after the administration of study medication. They defined as the primary outcome as ICU-free day at 28 days after randomization.

In HEAT study, study medication was used 8 times in acetaminophen group and 9 times is placebo group. Open-label acetaminophen was administered approximately 30% of patients in each groups. The difference of mean daily peak body temperature in the ICU was –0.25 ℃ (P<0.001). They found that there was trend to increase the ICU-free day at 28 days after randomization in acetaminophen group (median of 23 *vs.* 22 days, P=0.07). They also found that acetaminophen administration increased length of ICU stay in non-survivors and decreased it in survivors. There was no significant difference of mortality and length of stay both in ICU and hospital. The incidence of liver dysfunction was comparable between two groups.

The HEAT trial asked clinically relevant question and is largest randomized trial in this issue. This trial had planned well (20,21) and performed with excellent concealment and follow up. HEAT trial also had several limitations including high incidence of protocol violation and the use of open-label acetaminophen. Additionally the difference of body temperature between two groups was relatively small, which was maximized at Day 1 (about 0.5 ℃ difference between two groups), then disappeared after Day 3. This might be due to their protocol for the stop of study drug (they stopped it when patients body temperature was less than 37.5 ℃ for last 24 hours).

HEAT trial should be a mile stone study on the body temperature control in febrile critically ill patients. However, it is not the end of the story. Future study is necessary to address how long we should use the acetaminophen, how lower we should control body temperature, and what type of patients we should use acetaminophen.

HEAT trial tells us that the use of acetaminophen in infective critically ill patients is safe, but not affect to patients centered outcome. It might not be necessary to treat fever in ALL patients with suspected infection. We afraid that it might be reasonable to use acetaminophen in patients with fever related distress, as such a tachycardia and tachypnea. However, it is also acceptable not to use acetaminophen in patients that fever does not cause any stress response.

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Footnote

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Is there a role for continuous infusion of β-lactam antibiotics in severe sepsis?

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Sepsis is a leading cause of mortality and morbidity in critical care (1,2). There is an expanding literature examining optimal administration of β-lactam antibiotics in critically ill patients (3,4). The bactericidal and broad spectrum nature of β-lactams make them attractive in patients with sepsis. The time-over-MIC dependent killing with β-lactams would suggest benefit with administration as continuous infusion instead of intermittent dosing, particularly given the fluid shifts that occur in critically ill patients (5-7). Meta-analysis of studies comparing continuous infusions of β-lactams to standard intermittent dosing in acute infections have failed to find a consistent clinical benefit in mortality, infection recurrence, clinical cure, super-infection post-therapy, and safety outcomes in both critically- and non-critically ill patients (3,4,8-10). The question remains whether patients with severe sepsis will benefit (11).

Dulhunty *et al*. (the BLING II investigators) recently published "*A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis*", in a heterogenous critically-ill population (7). This was a well done, double-blinded, randomized (with good allocation concealment), controlled pragmatic trial conducted in 25 intensive care units in Australia, New Zealand, and Hong Kong, in adults with severe sepsis who were already being treated with a β-lactam antibiotic for <24 hours (median about 12 hours). The primary outcome was alive ICU-free days determined at day 28 after randomization; sample size was calculated to have 90% power to detect a difference of 3 days with α of 0.05. Secondary outcomes included: day-90 mortality, clinical cure at day 14 after antibiotic cessation, alive organ failure-free days at day 14, and duration of bacteremia post-randomization. The most common β-lactams used were piperacillin-tazobactam (69.3% continuous infusion, 71.4% intermittent infusion), and meropenem (29.7% continuous infusion, 27.3% intermittent infusion). Patients were well balanced in characteristics at baseline, and patients received the blinded study drug for a median of 3–4 days (until intensive care unit discharge). There was no difference in alive ICU-free days (18 *vs*. 20 days; P=0.38), in 90-day survival (74.3% *vs*. 72.5%; hazard ratio, 0.91; 95% CI, 0.63–1.31; P=0.61), clinical cure (52.4% *vs*. 49.5%; odds ratio, 1.12; (95% CI, 0.77–1.63; P=0.56), organ failure-free days (P=0.27), or duration of bacteremia (P=0.24), hospital length of stay, or adverse events between groups on intention to treat analysis.

This is the largest multicenter trial aiming to determine clinically relevant outcomes with continuous *vs*. intermittent infusion of broad spectrum β-lactam antibiotics in severe sepsis. Previous studies have found higher β-lactam serum concentrations with continuous infusion in critically ill patients with severe sepsis (12). The question has been whether this surrogate outcome translates to patient-relevant clinical benefit (11). There are reasons to think that it should be beneficial. For example, there is evidence that tissue levels of β-lactams in critically ill patients are lower than predicted from serum levels, and may be higher

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with continuous infusion (13-15). Given that β-lactams are hydrophilic, have a small distribution volume similar to extracellular water, and are predominantly excreted via the kidneys, one might expect a higher extracellular tissue level in critically ill patients who have capillary leak (resulting in expanded extracellular space) receiving continuous infusions (5,15). So, why might Dulhunty *et al*. not have found benefit to continuous infusion of β-lactams?

First, most patients in this study had lungs as infection source. In ventilator associated pneumonia (VAP) it is difficult to determine the organisms responsible for the infection, and it is possible that β-lactams were not optimal therapy for some. There is no clear gold-standard for diagnosis of VAP, and it is also possible that some of the patients may not have had sepsis at all. Second, most patients did not have bacteremia (81%), making it difficult to determine the responsible pathogen(s) and their MICs, particularly in patients who may have received their first doses of antibiotics prior to cultures (16). Third, the majority of the bacterial isolates were susceptible to the β-lactam used. With rising prevalence of more resistant gram-negative bacilli a benefit from continuous infusion of β-lactams to achieve longer time-above-MIC may emerge (2). Fourth, there is question whether continuous infusion of piperacillin-tazobactam actually achieves higher time-above-MIC than intermittent dosing (12). Future studies may consider a role for therapeutic drug monitoring to demonstrate differences between groups (5,12,14,15). Finally, those with septic shock may be a subgroup most likely to benefit from continuous infusion of β-lactams. There were many excluded patients, including those who had received antibiotics for >24 hours, and those where there was inability to randomize or prepare study medication, which may have excluded patients with the most severe sepsis and septic shock (14,15). Nevertheless, the results are similar to the previous BLING II study examining pharmacokinetics; in that trial, survival to hospital discharge was 90% in continuous *vs*. 80% in intermittent β-lactam infusion groups (P=0.47) (12). This previous trial had better clinical cure and survival outcomes; this may be explained by the higher severity of illness (including use of renal replacement therapy in 26% of patients) and fewer days on randomized therapy (3 *vs*. 5 days) in the current trial.

Where do we go from here? There are patient groups that may deserve further study. First, the growing population of patients with sepsis caused by gram-negative bacilli with increasing resistance patterns (1,13). Clearance of bacteremia in such patients is important, and longer duration of serum β-lactam levels >4× MIC provides optimal bactericidal effects. To safely achieve this with increasingly resistant gram negative pathogens, a continuous infusion may be required, particularly in those who have persistent bacteremia (5,14). Second, infections where tissue antimicrobial levels are more difficult to achieve, including meningitis, intra-abdominal abscess, and lung abscess (14). Third, patients very early in their episode of sepsis, with antimicrobials started in the first hour of presentation when there is highest likelihood of improving outcome (1). Finally, therapeutic drug level monitoring in patients with a known pathogen may allow determination of whether optimal pharmacodynamics are obtained in either group, and the relationship to clinical outcome (17,18).

At this time we do not suggest use of continuous infusion of β-Lactams in critically ill patients with severe sepsis. This is supported by the results of this trial, and previous meta-analyses (3,8-10). Further study may be required to define subgroups of patients that may benefit. A role for therapeutic drug monitoring of β-Lactams targeting time-above-MICs may be on the horizon (14).

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Balanced control of both hyper and hypo-inflammatory phases as a new treatment paradigm in sepsis

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Abstract: The immune response of the host against invading pathogens is clinically manifested as sepsis. Sepsis is a complicated process characterized by distinct phases that usually occur in a sequential manner. The initial hyper-inflammation helps in elimination of the pathogen, but potentially may lead to excessive tissue injury. Hypo-inflammation helps in restoring immune homeostasis, but may lead to significant immune suppression and death from secondary infections if not appropriately controlled. Immune-modulating intervention in sepsis should be based on a balanced control of both the hyper and the hypo-inflammatory phase.

Keywords: Sepsis; janus kinase; inhibition; cytokines; immune-suppression

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The immune response of the host against invading pathogens such as bacteria, fungi, and viruses is clinically manifested as sepsis. Sepsis is diagnosed when there is evidence for the presence of an infection and the host has clinical signs of the systemic inflammatory response syndrome (SIRS). Sepsis is characterized as severe when complicated by organ dysfunction, while septic shock is defined as sepsis with concurrent acute circulatory failure not responding to aggressive volume resuscitation.

Sepsis is the leading cause of death in intensive care unit (ICU) patients. Despite the significant improvements in supportive care and the prompt administration of broad spectrum empirical antimicrobial therapy, mortality rate is still around 30% (1).

Pathogenesis of sepsis

The pathogenesis of the septic process is extremely complex and involves a dynamic interplay between the pathogen and the host immune system. Although simplistic the immune response to sepsis can be divided in two distinct but overlapping phases (2). During the initial phase of sepsis, an over-activation of the immune system takes place in an effort to eliminate the invading pathogen. This hyper-inflammatory phase is mediated by a "cytokine storm" of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, and if left uncontrolled results in excessive tissue damage manifesting as septic shock and/or multi-organ dysfunction (MOD). Termination of the inflammatory process and restoration of immune system homeostasis occurs immediately after control of infection and is mediated by secretion of anti-inflammatory cytokines such as IL-10 (3). Prolonged or intensive hypo-inflammatory state may lead to immune effector exhaustion finally resulting in immune-suppression that is frequently observed in the late phases of sepsis (2). During this late immune-suppressive

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phase, patients may develop secondary infections such as ventilator associated pneumonia or bloodstream and other organ specific infections by weakly virulent pathogens such as Acinetobacter, Stenotrophomonas, Enterococus and Candida (4). Secondary infections result in repeated cycles of hyper and hypo-inflammatory phases further complicating the septic process. Additional evidence for the sepsis-associated immunosuppression is the high incidence of herpes virus reactivation that occurs in patients with prolonged septic episodes (5). These clinical observations are supported from *in vitro* data showing impaired cytotoxicity and increased apoptosis of immune effectors from septic patients (6).

Trials targeting the hyper-inflammatory phase of sepsis

Interleukin-1 receptor antagonist (IL-1Ra) is a plasma protein that inhibits both IL-1a and IL-1b after binding to the type 1 IL-1 receptor (7). Anakinra is a recombinant human IL-1Ra. The efficacy of Anakinra as an immune-modulator in patients with sepsis was compared with placebo in a double blind phase III trial. In this trial anakinra failed to prolong 28-day survival, but in a subgroup analysis survival was improved in patients with septic shock or MOD in the arm of anakinra (8). Based on these data a phase III trial testing the efficacy of anakinra in patients with septic shock and/or severe sepsis was conducted, and again failed to show any survival benefit (9). However, in a subgroup analysis IL-1 inhibition improved survival in patients with severe sepsis and features of macrophage activation syndrome (MAS) (10). The beneficial efficacy of anakinra in this group of patients should be clarified in a prospective randomized trial.

Most of the clinical trials conducted in the past were based on the notion that sepsis mortality was mainly due to an uncontrolled inflammatory response, and therefore were focused on testing the effect of blocking the hyper-inflammatory phase by using various agents including corticosteroids, and anti-endotoxin or anti-cytokine antibodies. These studies failed to show therapeutic benefit, and moreover in many cases excessive anti-inflammatory inhibition had a negative impact on the outcome of septic patients (11-13).

Reasons for failure of agents targeting the hyper-inflammatory phase

Failure of pro-inflammatory cytokine inhibition to improve the outcome of septic patients might be attributed to several reasons:

(I) Inhibition of the hyper-inflammatory phase needs to occur at the right time. Anti-inflammatory blockade should occur at the very beginning of the septic process and not at later stages where patients are already in a state of immune-suppression. Previous trials included patients admitted to ICU. Usually patients admitted to ICU are already in a late phase of the septic process with most of them having survived the initial hyper-inflammatory phase (14). Inhibition of pro-inflammatory cytokines in patients already in the late immunosuppressive phase might be detrimental. In accordance with the previous hypothesis is the fact that clinical trials using agents with the aim to block the initial pro-inflammatory phase showed some benefit in patients treated in early phase of sepsis, while the impact was detrimental in patients treated during the late imuno-supressed phase of sepsis (15);

(II) Moreover, inhibition of a single cytokine may not be effective simply because the function of one cytokine is counterbalanced by one or more of the other pro-inflammatory mediators acting in parallel;

(III) Another important issue is the intensity of inhibition, since a certain degree of inflammation is required for the effective clearance of the pathogen. Complete blockade of the hyper-inflammatory phase might have detrimental effects because of the inability to eliminate the pathogen. In conclusion, absence of fine control and monitoring of the inhibition in a time specific manner may contribute to the failure of anti-inflammatory trials.

The significance of a fine balance between pro and anti-inflammatory phases, and the association with outcome has been shown convincingly in an animal model of sepsis induced by cecal ligation and puncture (CLP). A hyper-inflammatory immune response mediated by an excessive amount of pro-inflammatory cytokines is observed in severe sepsis and is associated with increased mortality, whereas a more balanced immune response with a more pronounced anti-inflammatory phase is associated with less severe sepsis and reduced mortality. Increasing the pro/anti-inflammatory ratio by administering an anti-IL-10 antibody increases death rate, while decreasing the pro/anti-inflammatory ratio by exogenous administration of IL-10 results in increase survival. Thus, the fine balance between the pro and anti-inflammatory mediators is closely related to severity and

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outcome of sepsis (16).

The significance of the balance between pro and anti-inflammatory cytokines in the outcome of sepsis has been shown also in human studies. In a previous study including patients with sepsis a TNF-α/IL-10 ratio during the first 48 hours equal to one is a good predictor of improved outcome (17).

Prevention of immune suppression associated with sepsis

As already mentioned most of the patients admitting in ICU have survived the hyper-inflammatory stage and are already in a state of immune-suppression and in risk for secondary infections. Since immune-suppression is considered as a significant contributor of sepsis mortality, harnessing the host immunity by various agents is a reasonable alternative. Based on this notion, previous trials attempted to shorten the degree and the length of the immune-suppressive phase by using immune-stimulators such as interferon-gamma (IFN-gamma), granulocyte macrophage colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor (G-CSF). However, the clinical benefit produced by these agents was modest (18,19).

A promising cytokine with an immune stimulating effect and the ability to restore immune function in various diseases is interleukin-7 (IL-7). IL-7 is a cytokine with a pleotropic action on various immune cell subsets including proliferation of both naïve and memory T-cells. Administration of IL-7 to patients with cancer and HIV infected patients resulted in significant increase of peripheral blood CD4 and CD8 without expansion of the T-regulatory cell pool (20). The immune stimulating effect and the good safety clinical profile makes IL-7 a promising agent that need to be tested in future clinical trials in sepsis patients.

Recently the scientific interest has focused on the manipulation of immune checkpoint inhibitors for the treatment of patients with cancer. An interesting observation in patients with sepsis is the increased expression of PD-1 on T-cells as an important mediator of the immune-suppressive phase. Indeed, animal studies have already shown that blocking of PD-1/PD-L checkpoint results in improved survival of the septic mice (21). Moreover, human trials have shown that PD-1 overexpression is associated with impaired T-cell function and mortality from secondary infections in patients with established sepsis (22). These data suggest that blocking immune checkpoints with the aim to prevent sepsis-associated immune-suppression is a promising therapeutic option that deserves testing in human clinical trials.

Balanced monitoring of both hyper-inflammatory and immunosuppressive phase

Pro-inflammatory and anti-inflammatory cytokines mediate their effect through a common downstream signaling pathway that consists of different tyrosine kinase of Janus family (JAKs) interacting with signal transducer and activator of transcription (STAT) proteins. Inhibition of JAK proteins theoretically offers the potential for a global immune-modulation affecting both phases of sepsis, e.g., preventing the excessive tissue damage associated with hyper-inflammation and the over expression of anti-inflammatory cytokines resulting in immune paresis and death from secondary infections. Ruxolitinib (Ruxo), a JAK1 and JAK2 small molecule inhibitor recently approved for the treatment of patients with primary and secondary myelofibrosis, is a candidate drug for testing in future clinical trials (23).

In a previous study performed by our team, we examined the effect of Ruxo in a mouse model of sepsis due to Candida albicans. Fungal loads and inflammation scores were determined in various affected organs, while levels of pro and anti-inflammatory cytokines were measured in the serum of infected animals. Mice infected with Candida were treated with increasing doses of Ruxo (1.5–50 mg/kg). An inverted-U correlation between Ruxo dosing and median survival time (MST) was observed. High dose Ruxo was associated with the worst survival, while progressive de-escalation of dosing resulted in gradual increase of MST. Low dose (6.25 mg/kg) Ruxo produced the best survival and mice treated with this dose had increased survival as compared with control animals. The therapeutic benefit of Ruxo was lost after further reduction of dose. Thus, low dose Ruxo (6.25 mg/kg) was found as the optimal dose for treatment of septic mice. Mice treated with high dose Ruxo had the higher fungal loads and lower inflammation scores as compared with control mice, meaning that intensive abrogation of the inflammatory phase results in overwhelming infection. On the contrary, mice treated with the optimal dose of Ruxo had the same fungal load but lower inflammation score as compared with placebo, meaning that increased survival is due to prevention of excessive tissue injury and not to an antifungal effect of the study drug. Interestingly, mice treated with the optimal dose of Ruxo had a balanced serum TNF-α/IL-10 ratio equal to one, as a further proof of the concept that a balance between pro- and anti-inflammatory signalling is required for a successful outcome (24).

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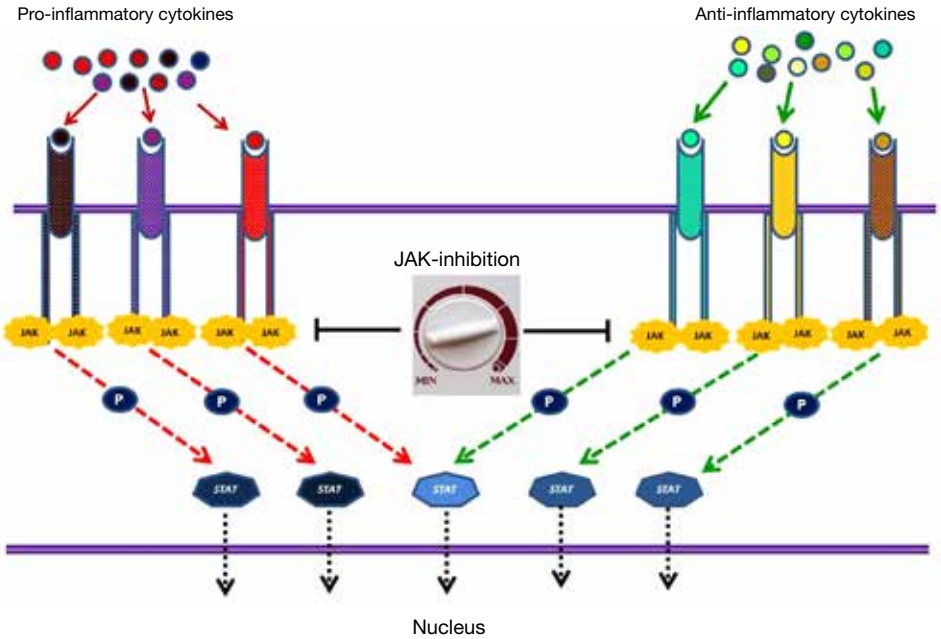

Figure 1 Binding of pro and anti-inflammatory cytokines to specific receptors expressed on the cell surface results in activation of JAK-STAT signal transduction pathway. Janus tyrosine kinase family consists of four non-receptor kinases (Jak1, Jak2, Jak3, and Tyk2). Activated JAKs recruit and phosphorylate STAT proteins. STAT family consists of seven functionally related proteins (Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b, and Stat6). Activated STATs dissociate from the receptor, dimerize and translocate to nucleus and regulate gene expression. Various cytokines activate different JAK-STAT complexes and result in characteristic gene expression patterns. JAK inhibition results in downstream signaling blockade of all pro and anti-inflammatory cytokines. Moreover, escalating or de-escalating the dose of JAK-inhibitor offers the unique possibility of balanced monitoring of both pro and anti-inflammatory phases in sepsis. JAK, kinase of Janus; STAT, signal transducer and activator of transcription.

Conclusions

Data from animal studies support the concept that any immune-modulating intervention in sepsis should also take into account the immunosuppressive phase that may be exacerbated by an uncontrolled inhibition of the early hyper-inflammatory phase. Balanced monitoring of both phases may result in prevention of excessive tissue damage through control of hyper-inflammation and without leading to significant immune-suppression (*Figure 1*). Administration of agents with immune-stimulating activity such as IL-7 and immune checkpoint inhibitors, with the aim to alleviate immune-suppression should be tested in clinical trials. Inhibition of the JAK-STAT pathway is another therapeutic target with promising efficacy in animal studies. The efficacy of Ruxolitinib as an immune-modulator in sepsis should be further tested in human trials.

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Footnote

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Septic shock in the era of precision medicine

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Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persistent hypotension requiring vasopressors to maintain MAP >65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation (1). The treatment include combined regimens of antibiotics, source control and hemodynamic resuscitation.

Although recent studies described decreasing mortality rates in critically ill patients with septic shock, the overall hospital mortality remains high. Five subsets of septic shock have been identified, being the combination of refractory hypotension with hyperlactacidemia associated with poor survival, in spite of aggressive management. It should be denoted that hypotension should be defined as a mean arterial pressure less than 65 mmHg according to the pragmatic decision that this was most often recorded in datasets derived from patients with sepsis (2).

Lamontagne *et al.* (3) conducted a pilot trial to inform the design of a larger trial examining the effect of lower versus higher mean arterial pressure (MAP) targets for vasopressor therapy in shock. The authors randomized assigned critically ill patients who were presumed to suffer from vasodilatory shock regardless of admission diagnosis to a standard (60–65 mmHg) versus a higher (75–80 mmHg) MAP target. Other aspects of management, such as sedation and volume status assessment, are also potential confounders in the hypotension-vasopressor relationship, but were not assessed. A total of 118 patients were enrolled from 11 Canadian centers. Overall mortality risk was not different between standard and "intensificated" reanimation intervention. Whereas it was not documented in younger patients, among patients aged 75 years or older, an "intensificated" management to get a higher MAP target was associated with increased hospital mortality (60% *vs.* 13%, P=0.03). Moreover, risk of cardiac arrhythmias increased near two-fold (36% *vs.* 20%, P=0.07) when vasoactive agents were prescribed to get "supranormal" values. A trend of higher ischemic events in elderly with supranormal resuscitation is also reported. No information was provided in the effect of age in arrhythmias.

The study has some imbalances and peculiarities, for instance 48% use of vasopressine. A difference in 13% in septic shock, different infectious sites [double prevalence (12% *vs.* 23% for pneumonia] and differences in acute pancreatitis (additional 5%). Differences in chronic hypertension (33% *vs.* 57%), in albumin infusion (49% *vs.* 64%) and significant differences in red cells packed transfusion needs (49% *vs.* 71%, P=0.024) should be noted.

Their findings underscores the concept that optimal MAP targets may vary across specific patient subgroups (4). Indeed, at the bedside, it is a common practice titrate the need of volume resuscitation and norepinephrine to the urine output. This is indeed, an approach based on the more modern concept of "Precision" or "Personalized" medicine (5). Other variables, including other tissue perfusion markers (e.g., base deficit, acute alteration in mentation, venous-arterial PCO_2 gap), resuscitation end points (central venous saturation, lactate clearance) or blood pressure characteristics (e.g., diastolic pressure) could potentially

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improve on the proposed targets to optimize outcomes.

In septic shock patients, beyond the selection of a suitable antibiotic, the administration of an appropriate antimicrobial dosing regimen (dose and schedule) influences the probability of success. Patients with more energetic resuscitation present higher positive volume infusion balance and this is associated with an increase in the volume of distribution (6,7). This condition might be associated with therapeutic underdosing, delaying to get recommended plasma concentrations of antibiotics above the minimal inhibitory concentration of the responsible pathogen, requiring therapeutic drug monitoring and higher doses of antimicrobials.

Identification of a critically ill patient with shock would benefit from obtaining serum lactate measurements, both to stratify and to monitor the response to therapy (8). However, serum lactate measurements are not universally available, especially outside the ICU or in low and medium income countries (LMIC). And it time to move forward from lactate measurement to proteomics and genomics, because the core problem is a mitochondrial dysfunction.

It is cornerstone to acknowledge that current therapies are likely effective only in some subgroups during specific phases of diseases. Advanced age, like in the OVATION trial (3), is an example. Incorporating theranostics, to individualize different therapeutic approaches depending of the host is an urgent need. The concept of "Precision Medicine"—prevention and treatment strategies that take individual variability into account—has been well developed in chronic diseases, such as diabetes mellitus. The prospect to apply this concept has been dramatically improved. It is urgently needed the development of large-scale biological databases, newer methods for characterizing patients (proteomics, metabolomics, genomics, cellular assays), and recent computational tools to assess large data sets. Advances in basic research, including molecular biology, genomics and bioinformatics are largely applied to cancer (9). Next steps should be to translate this experience to sepsis and septic shock, being crucial to incorporate the inherent concept of diversity to patients requiring vasopressors.

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Sepsis without SIRS is still sepsis

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The host response to infection is pivotal to the clinical features observed in a patient with sepsis. Indeed, Sir William Osler noted that "*Except on few occasions, the patient appears to die from the body's response to infection rather than from it*". Importantly, evidence of the host response, in the form of the systemic inflammatory response syndrome (SIRS), during a documented or suspected infection is required criteria for sepsis diagnosis. Currently, the consensus for sepsis diagnosis, based on expert opinion, requires evidence of SIRS based on two or more of the following signs, abnormalities in white blood cell count, fever or hypothermia, tachycardia or elevated respiratory rate. Unfortunately, these criteria have never been validated and therefore the diagnosis of sepsis may include a heterogeneous population of patients, potentially with various pathophysiology and different outcomes, who may also benefit from distinct therapeutics. However, the mechanisms of sepsis remain uncertain. Given the need to standardize sepsis diagnostics, the SIRS plus infection criteria was embraced by the clinical and research community.

To better our understanding of the SIRS criteria in defining sepsis, Kaukonen *et al.* (1) conducted a retrospective investigation of patient data from a database available to the Australian and New Zealand Intensive Care Society (ANZICS). Specifically, they were interested in assessing how well the requirement of at least two SIRS criteria performed in diagnosing severe sepsis. They hypothesized that requiring two criteria to establish SIRS has low sensitivity and validity such that populations of patients, who ultimately have severe sepsis and organ dysfunction, are improperly diagnosed. To test this hypothesis they decided to quantify the number and clinical outcomes of patients admitted to an intensive care unit (ICU), who had an infection and organ dysfunction but lacked two or more SIRS signs. Additionally, they tested if there was a difference in the risk of death between patients who had two criteria *vs.* one, as is expected if the requirement of two criteria to establish a diagnosis has validity.

Data was reviewed from 1,171,797 patients admitted to 172 ICUs over a 14-year period. Records for patients admitted with a potential or proven infection using APACHE III information were included. Severely septic patients were determined from diagnostic admission codes for infection and organ failure. SIRS criteria were applied to the study data and in-hospital mortality was assessed. Patients with severe sepsis were divided into those who had two or greater SIRS criteria (SIRS-positive severe sepsis) *vs.* those who had less than two SIRS criteria (SIRS-negative).

Infection and organ dysfunction were identified in 109,663 patients, accounting for approximately 10% of patient records. SIRS-negative patients represented 12.1% of severe sepsis. Overall, the SIRS-negative population was older, less ill and had better overall mortality. One in five SIRS negative patients had no SIRS criteria while an abnormal white blood cell count was the most common single SIRS criteria found in the SIRS-negative group.

When they examined if two SIRS criteria significantly represented a transition point in patient outcome, they found that each criteria incrementally increased mortality by 13%, with no additional change when the level of two criteria was reached. Hence, diagnostically there is no data to support the requirement of two SIRS criteria for defining severe sepsis.

This trial is important evidence supporting what many researchers in the area have speculated for decades, namely that the sepsis syndrome is not well understood. In particular, this report generates a number of interesting possibilities. First, sepsis may not represent a gradient of severity starting as simple infection and progressing to septic shock. Each presentation may be due to different mechanisms. This is important, as different therapeutics

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may be necessary for different variations of disease. Secondly, patients with the same level of sepsis severity may also have different underlying pathophysiology resulting in similar clinical phenotypes. As an analogy, acute coronary syndromes are defined by the presence or absence of blood troponins in conjunction with EKG changes. However, if patients were only categorized by the presence of chest pain and a number of clinical signs such as tachycardia or tachypnea without any additional diagnostic tests, the result would be a heterogeneous population of heart attacks, pulmonary embolisms, pneumonias, aortic dissections and chest wall pain. Treating this group with the same therapeutic, for example thrombolytics, could lead to some patients improving and may even result in a positive clinical trial. Clearly, this approach would lead to major issues, with some patients experiencing no benefit, or worse, harm. The addition of troponins have altered the way heart attacks are classified, risk stratified and treated, leading to patient improvements. The key component of this success is the fact that the diagnostic test is a directly related to the pathophysiology. In other words, cardiac ischemia leads to myocyte damage causing a leak of the troponin protein into the blood. This type of diagnostic advancement is a critical component missing in sepsis research and clinical care.

The article by Kaukonen and colleagues (1) proves what we have known for many years that clinical information alone will miss individuals with even severe sepsis. This strongly suggests that we should move beyond just clinical indicators of sepsis, moving into the realm of personalized or precision medicine to help include individuals who would otherwise be missed using clinical data only. Over the last 10-15 years, there have been many advances in the use of precision medicine for diagnosis and prognosis of disease (2). Although originally used for cancer diagnosis, prognosis and assisting in therapeutic decisions, it is now being used for a host of other diseases including sepsis (2). This type of investigation looking for phenotypic clusters or endotypes has yielded important information in sepsis, whether it is using just clinical data to determine phenotypes (3), using genomics data in children (4), using metabolomics data in adults (5,6) or children (7,8), or using cytokine-based risk stratification in adults (9,10).

Thus, there are tools being developed today to detect septic patients who may not show all the clinical features of sepsis, to help subclassify endotypes or phenotypes of sepsis for prognosis and help direct therapy or at least help in sepsis therapeutic research. There is great promise in this direction for the future of sepsis diagnosis and treatment.

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Footnote

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Why we need a new definition of sepsis

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Abstract: On April 23, 2015, Kaukonen and colleagues published an article in the *New England Journal of Medicine* entitled "Systemic inflammatory response syndrome criteria in defining severe sepsis", which investigated the sensitivity and validity of using SIRS criteria to define intensive care unit (ICU) patients with severe sepsis. This study used admission data of over 100,000 patients in order to investigate patients with severe sepsis who either met or didn't meet SIRS criteria. The investigators found that in-hospital mortality increased linearly with the number of SIRS criteria met; raising concern that SIRS criterion is not sensitive enough. This study of SIRS criteria raises important questions about the recognition and diagnosis of severe sepsis.

Keywords: Sepsis; systemic inflammatory response syndrome (SIRS)

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The systemic inflammatory response syndrome (SIRS) was described by the American College of Chest Physician and Society of Critical Care Medicine in a consensus statement from 1991 as part of a larger effort to uniformly define sepsis (1). The aim of this recently published study by Kaukonen and colleagues, "Systemic inflammatory response syndrome criteria in defining severe sepsis", was to assess the sensitivity and validity of using SIRS criteria for this purpose. This study evaluated patients whose clinical presentation suggested severe sepsis, comparing those who met SIRS criteria to those who did not meet SIRS criteria. The study was a remarkable effort involving review of over 1 million patients cared for in Australian and New Zealand intensive care units (ICUs) from 2000 to 2013, accounting for approximately 90% of all ICU admissions in this area during this time (2). The primary outcome was in-hospital mortality, with a secondary outcome being place of discharge (home, rehab or other hospital). The hypothesis was that there would be a linear increase in the risk of death, not a defined transition point after two criteria (the definition of meeting SIRS criteria). In studying over 100,000 septic patients, the investigators found no real transitional increase at two criteria, which raises questions on the sensitivity and validity of using SIRS to define severe sepsis.

When SIRS criteria were initially defined more than 20 years ago, the goal was to provide a "practical framework" for use in clinical practice as well as in research settings (3). Prior to these definitions, there was limited uniformity to sepsis definitions used across research teams, leading to difficulty with generalizing findings (4). Criteria for SIRS included specific changes in body temperature, heart rate, tachypnea or hyperventilation and white blood cell count, with two or more of these being necessary to label the patients with SIRS. Sepsis was defined as a subcategory of SIRS patients who had a documented or suspected source of infection. Severe sepsis narrowed this category to patients with organ dysfunction, and septic shock was a subcategory of severely septic patients with hypotension. These criteria and thresholds were chosen by expert consensus, with the goal to have some standardization across medical centers and research groups. Data at the time showed higher risk of mortality for patients meeting these criteria on ICU admission (1). These definitions of SIRS, sepsis and septic shock has been used clinically and throughout research studies for the past few decades, but have evoked considerable controversy (4-9). SIRS criteria was a clinical syndrome description, and as such may combine several distinct pathophysiological pathways (5,9). Septic patients

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who do not fulfill SIRS criteria may be excluded from sepsis investigations, and may receive a delay in appropriate treatment. Kaukonen and colleagues have made a significant contribution by investigating the clinical outcomes for this group of patients who would otherwise be excluded by the SIRS definition.

This study aimed to evaluate sensitivity, face validity and construct validity of SIRS. Sensitivity is the ability of a test to recognize true positives, while specificity measures number of true negatives correctly identified. In a screening test for a potentially life-threatening disease, such as severe sepsis, high sensitivity would be valued over high specificity so that cases are not missed. An important concern raised by this study is that one in eight patients with sepsis is missed by the SIRS criteria, indicating an undesirably low sensitivity. Investigators have also criticized SIRS criteria for the lack of ability to differentiate between septic and non-septic patients (poor specificity) (10). The face validity refers to the transparency or relevance of a test as it appears to test participants, i.e., that the test looks like it is going to measure what it's supposed to measure (11). Examining the face validity requires some idea of what those using the test believe it should show. Construct validity indicates the degree to which a test measures what it purports to measure. Although the study did not explicitly study or quantify how much the SIRS criteria contribute to making a diagnosis of sepsis, it is a reasonable inference that many critical care clinicians use SIRS criteria in their diagnosis of a septic patient. However, SIRS criteria are not required for a diagnosis of sepsis (contrary to the 1991 consensus definition), as some patients were labeled as SIRS-negative and simultaneously identified by clinicians as having sepsis. SIRS was not designed to measure illness severity or short-term sepsis mortality but was designed to be exquisitely sensitive in not missing patients with sepsis, and therefore is lacking in construct validity.

A central limitation of all studies of severe sepsis is that there is no accepted gold standard for a definition of severe sepsis. Kaukonen's study, although excellent, is not immune to this limitation. The designation of severe sepsis was limited to information obtained in the first 24 hours of ICU admission and based on coding at that time: severe sepsis was defined as having APACHE III diagnoses of infection plus at least one organ failure or APACHE III diagnoses of severe sepsis or septic shock. Therefore, the diagnosis of sepsis in this study is really a definition based on coding and APACHE III diagnoses, a method which may have inherent limitations, much like the 1991 consensus definition that relies on SIRS.

Patients labeled as SIRS-positive severe sepsis met two or more SIRS criteria in addition to these criteria for severe sepsis, while SIRS-negative severe sepsis met less than two SIRS criteria. Pneumonia, gastrointestinal rupture, and biliary infection were common diagnoses (18.2%, 18.5% and 10.4%, respectively) among the SIRS-negative patients. Of SIRS-negative patients, 20% (n=2,624) did not meet any SIRS criteria. This group had a high proportion of patients with septic shock (33%, n=866) or mechanical ventilation (51%, n=1,329). Although these proportions may seem high, they represent a very small percentage of all patients. Only 0.8% of patients with septic shock and 1.2% of patients with mechanical ventilation had zero SIRS criteria. Taken together, the data suggest that clinicians are more likely to diagnosis a SIRS negative patient with sepsis if they have severe organ failure, such as shock or respiratory failure, or if there is evidence of a disease that is highly associated with infection. Like all studies that rely on clinical registry surveillance, data were gathered by collectors in the ICU as part of a routine process, which is by design susceptible to missing information as well as misclassification. However, individual validation of whether all 1.2 million patients were appropriately categorized is infeasible. Similarly, in a study of this magnitude, there is no feasible mechanism by which one could identify all patients that were incorrectly excluded from the study.

It is difficult to identify patients with severe sepsis in a way that allows classification for both clinical care and research purposes. Reliance solely on SIRS criteria may be insufficiently sensitive, and is certainly not specific. Therefore, there may be value in using a screening test for sepsis (highly sensitive) and a confirmatory test (highly specific). SIRS has never been very specific (12) and was not designed to be so. Sepsis and SIRS criteria have been reevaluated by the Surviving Sepsis Campaign and the diagnostic criteria for sepsis were significantly expanded to include an extensive list of other indicators of infection, inflammation, hemodynamic abnormalities or organ dysfunction (13-16). The myriad indicators of sepsis in the revised definition may increase sensitivity, but the need for specificity remains unfulfilled. As a response, several biomarkers have been investigated for use in confirming the diagnosis of sepsis, including procalcitonin, C-reactive protein, tumor necrosis factor-α, various interleukins and protein C (7). Procalcitonin may have the most utility for identifying an infectious cause of SIRS (7,17) and there have been suggestions for using procalcitonin levels to

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classify sepsis and grade severity (18). Testing to this point indicates that procalcitonin is more sensitive and less specific, depending on cutoff values used (19,20). However, these biomarkers remain investigational, and have yet to be validated sufficiently for widespread clinical use.

We believe that future directions for improving identification of sepsis may rely on more complex quantification. The SIRS definition is simple clinically and is an easy set of inclusion criteria for sepsis research (21-23). However, the clinician, when diagnosing sepsis, is likely subconsciously applying a Bayesian algorithm that includes the SIRS criteria as well as several other clinical parameters, such as severity of disease (for example, giving more weight to a white blood cell count of 21,000 *vs.* 11,000 cells/μL) or known diseases that confer a high probability of sepsis (i.e., intestinal perforation). A complex algorithm that attempts to recognize this clinical syndrome may prove superior to more conventional definitions. Several other scoring systems have improved accuracy by weighting continuous *vs.* dichotomous data, such as the eCURB *vs.* the CURB-65 for scoring pneumonia (24). Complex Bayesian scoring systems would require a computer, ideally, to quickly acquire and process several clinical data from the patient's record and produce a diagnostic probability of sepsis. The data acquired from Kaukonen and colleagues' study is an excellent resource that could be used to develop and test such systems.

The results of Kaukonen and colleagues' study demonstrate that the SIRS criteria are flawed in recognizing sepsis. The results of this study will likely not directly change clinical practice, as clinicians are already diagnosis sepsis by rules that differ from the 1991 consensus statement, which implies that there is already recognition among clinicians that the SIRS criteria are limited. Perhaps some clinicians, upon reading this study, will be reminded that patients who do not meet SIRS criteria still may have significant morbidity and mortality. However, the true value of this study is the insight it affords in future leaders of critical care in designing new criteria for recognition of sepsis. This study should be a call to arms that critical care physicians and hospitals need to develop a better screening tool than the current one. The future diagnostic method will likely employ large, multidimensional clinical data obtained from the medical record and Bayesian algorithms to arrive at an improved determination of sepsis.

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Footnote

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Forget skin scrubbing and other antiseptics: prevent catheter related infections using chlorhexidine plus alcohol

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One of the fundamental interventions that we as clinicians perform on critically ill patients is vascular access. Fluid resuscitation, drug administration, intravascular pressure monitoring, blood gas analysis and hemodialysis are just some of the numerous interventions necessary for survival and better patient outcome. Sadly, there are risks for every well intended intervention and in vascular access the most important one is infection. Millions of patients require these catheters yearly and roughly 5% will develop a catheter-related infection (CRI); up to 35% of those who do, will subsequently succumb to that infection (1,2).

International guidelines for the prevention of intravascular CRIs favor using chlorhexidine-alcohol (CHG-OH) solutions for skin preparation before insertion of central venous catheters and peripheral arterial catheters (3) although they acknowledge the lack of a formal comparison between povidone-iodine plus alcohol (PVI-OH) and CHG-OH; they have left this as an unresolved issue.

A common practice during skin preparation is scrubbing the skin with a detergent before the antiseptic application; although published evidence of its effectiveness is scarce many centers do this as a standard of care.

Recently the CLEAN trial published in *Lancet* (4) sought to explore the effectiveness of the aforementioned antiseptic solutions with or without skin scrubbing prior to the antiseptic. In this well designed trial by Olivier-Mimoz *et al.* the authors compared in a multicenter ICU setting the use of CHG-OH *vs.* PVI-OH (with or without skin scrubbing) in the prevention of CRIs, catheter-related bloodstream infections (CR-BSI) and catheter colonization. Nearly 2,350 patients were enrolled with a total of 5,159 catheters placed. The patients were randomized properly and no differences in patient's characteristics were seen in any of the groups.

The authors defined catheter colonization as a quantitative catheter-tip culture showing at least one microorganism in a concentration of at least 1,000 CFU per mL. Catheter-related sepsis without bacteremia as a combination of fever or hypothermia and catheter colonization with resolution of fever or hypothermia within 48 h after catheter removal and without any change in antimicrobial therapy. CR-BSI, as a combination of fever or hypothermia with one or more positive peripheral blood cultures, drawn 48 h before or after catheter withdrawal; isolation of the same organism from the colonized catheter or from the catheter insertion site or a blood culture differential time-to-positivity of 2 h or more, and no apparent source of bacteremia other than the catheter. CRIs were either catheter-related sepsis without bacteremia or CR-BSI.

The study clearly demonstrated a hazard ratio reduction favoring CHG-OH for catheter colonization compared with PVI-OH, regardless the type and severity of the patients and irrespective of the type of catheter and site of insertion. The study also demonstrated a significant statistical difference favoring CHG-OH for the reduction of CRI and CR-BSI in patients with hemodialysis catheters and arterial catheters, but the group of central venous catheters failed to show reduction in these end points. Only subclavian venous catheters were favored by CHG-OH; femoral and internal jugular catheters were not associated with infections' reduction.

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The authors stated that there was a similar effect on Gram positive and Gram negative bacteria. Although using the tables provided in the appendix we found that patients in the CHG-OH group had less colonization by Gram-positive bacteria than the PVI-OH group (53.5 *vs*. 80.8, *P*=0.0001). No differences were observed in the CRI and CR-BSI associated with Gram-positives or any other microorganism; and even in colonized catheters the number of colonies was significantly lower in patients under de CHG-OH protocol. Many studies have shown (5,6) a higher impact on gram positive bacteria when chlorhexidine is used in ICU, but more recently studies have also shown a favorable impact on other pathogens especially in multidrug-resistant Gram-negative rods (7,8).

The other main finding of this study is that skin scrubbing with detergent had no impact on any of the primary or secondary outcomes related to infection. It is common that in any invasive procedure health care providers scrub the skin in order to remove excess biological material and dirt; this is the first study that demonstrates that this has no impact the patient's outcome, at least infection wise, but let us not generalize the word "scrubbing"; scrubbing of catheters' ports play a strong role in the in infection's prevention; antiseptic scrubbing combined with personal protective equipment (PPE) when handling these ports reduce the likelihood of infection (9) and it is important to point out that the trial did not make a formal analysis on the type of antiseptic used for this purpose, the number of medications, manipulations of the ports, adherence to antiseptic scrubbing and PPE leaving these actions unresolved. The lack of formal audits for adherence as described in the discussion leaves room for improvement and further studies in this topic, it also raises the question of the exact time when the breach for colonization and/or infection took place; was it during insertion or during the following days after insertion?

We found interesting that approximately one fourth of catheters were inserted femoral. This is probably due to the diversity of catheters studied, since this trial included arterial, venous and hemodialysis catheters. For jugular and femoral insertion sites a higher risk of infections has been well described (10,11). Some studies while attempting to reduce CRI only involved a small number of patients with venous femoral access (12) this is important while taking into account the subgroup of patients with a central venous access compared with arterial or hemodialysis catheters.

It would have been favorable if the study had divided the catheters by the number of lumens and additionally clarified which patients were under total parenteral nutrition, since these two factors have been implicated with a higher incidence of infection (13). We speculated that in the group of central venous access there were a low percentage of patients with total parenteral nutrition since roughly the duration of catheters was 3 to 11 days.

As with any infection prevention trial one of the most important outcomes is infection related mortality and length of hospital stay, and amend economic cost. The trial did not show a difference in both of these outcomes in patients assigned to either antiseptic solution or scrubbing.

Without a doubt the findings by Olivier-Mimoz and his group make any ICU that still use povidone or chlorhexidine alone for skin preparation reconsider this topic and to start reading the labels. For preventionist lower colonization ultimately leads to lower infection rates and these results help support many administrative decisions regarding cost reduction and patient safety. Finally, we believe that this trial will pave the way for a more robust and solid evidence background for future prevention guidelines.

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Footnote

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A multimodality approach to prevent catheter-related bloodstream infections: the role of chlorhexidine-alcohol as a skin antiseptic before intravascular catheter insertion

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Health care-associated infection is an increasing threat to patient safety. Over 400,000 patients in the intensive care units (ICUs) and 1.2 million patients outside the ICUs were affected by hospital care-associated infections, with >30,000 deaths attributed to hospital care-associated bloodstream infections in United States in 2002 (1). Intravascular catheters play a pivotal role in the management of both ICU and non-ICU patients, but inadequate infection control precautions in using these devices may lead to catheter-related bloodstream infection (CR-BSI) resulting in prolonged hospital stay and excessive mortality (2). As such, having the best strategy to prevent CR-BSI has a potential huge benefit on both patient outcome and healthcare cost (3).

Most intravascular catheters used in the ICUs are non-cuffed and for short-term purposes, extraluminal catheter colonization derived from the cutaneous microflora is believed to be the main mechanistic cause of CR-BSI (4). With this pathogenic mechanism in mind, strategies achieving successful eradication of cutaneous bacteria, both before and after intravascular catheter insertion, would be expected to be effective in reducing CR-BSI. Consequently, the CLEAN trial assessing whether skin scrubbing, in combination with using either chlorhexidine-alcohol or povidone iodine-alcohol as skin antiseptic, is effective in reducing CR-BSI has paramount importance (5).

Methods

The CLEAN trial is an open-label, multicenter, randomized-controlled, two-by-two factorial trial. The factorial design aimed to answer three clinical questions using the same cohort of patients, including (I) is skin scrubbing before intravascular catheter insertion more effective than no skin scrubbing in preventing CR-BSI; (II) is chlorhexidine-alcohol more effective than povidone iodine-alcohol as a skin antiseptic before intravascular catheter insertion in preventing CR-BSI; and (III) does skin scrubbing work better only with a particular type of skin antiseptic (chlorhexidine-alcohol or povidone iodine-alcohol)? The study had 80% power to detect a 50% relative risk reduction in CR-BSI after using chlorhexidine-alcohol as skin antiseptic compared to povidone iodine-alcohol, assuming the baseline risk of CR-BSI in the povidone iodine-alcohol group was 5%. This was a well-designed study, including 2,349 patients (1,181 patients were randomly allocated to chlorhexidine-alcohol: 594 patients with scrubbing, 587 without; 1,168 to povidone iodine-alcohol: 580 patients with scrubbing, 588 without) from 11 French ICUs in six hospitals.

Internal validity was achieved by adequate allocation concealment through web-based randomization stratified by center, and the primary outcome, catheter-related infection

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and CR-BSI, was determined by microbiologists masked to group assignment. The external validity of the trial was less certain; study patients were predominantly medical patients with a substantial proportion of them with underlying immunodeficiency (6%), haematological malignancy (6%) and metastatic cancer (6%).

Findings

The average length of the intravascular catheter left in-situ was 6 days (interquartile range, 3-11 days). Chlorhexidine-alcohol was associated with a reduced risk of CR-BSI (0.7%) [0.28 *vs.* 1.32 per 1,000 catheter-days with povidone iodine-alcohol (1.1%); HR =0.21; 95% CI, 0.07-0.59]. Scrubbing was not associated with a significant reduction in catheter colonization or CR-BSI. Although systemic adverse events were not observed, severe skin reactions did occur more frequently in chlorhexidine-alcohol group (3%) than povidone iodine–alcohol group (1%). Despite a reduction in incidence of CR-BSI in the chlorhexidine-alcohol group, there was no significant reduction in length of stay or mortality.

Commentary

Extraluminal colonization is the predominant mechanism of CR-BSI related to short-term non-cuffed intravascular catheters (4). Chlorhexidine is a synthetic bisbiguanide that binds to cutaneous protein resulting in a persisting antimicrobial effect with limited systemic absorption. It has bacteriostatic, bactericidal and fungicidal activity towards a wide range of micro-organisms (6). In line with the perceived benefits of chlorhexidine, the CLEAN study has confirmed that (I) chlorhexidine-alcohol was a more effective skin antiseptic than povidone iodine-alcohol, and (II) a two-step skin cleaning process by adding skin scrubbing did not provide further improvement in skin decolonization and any subsequent catheter colonization and infection compared to an one-step skin cleaning process before intravascular catheter insertion.

Previous studies showed that CR-BSI was associated with a significant attributable morbidity and mortality in critically ill patients (2,3). So, why this study could not demonstrate any substantial reduction in length of stay or mortality despite a significant reduction in CR-BSI after using chlorhexidine-alcohol as a skin antiseptic before intravascular catheter insertion? First, this study was not powered to detect a mortality or length of stay difference between the two groups. Second, the incidence of CR-BSI in the povidone iodine-alcohol group (1.1%) was much lower than the assumption (5%) in the sample size calculation. This result suggests that the study protocol itself, regardless of the intervention allocated, was effective in reducing risk of CR-BSI. The elements of the protocol that may be effective in reducing CR-BSI include (I) the physician who inserted the catheter disinfected the skin used maximal barrier precautions; (II) the antiseptic was applied to the skin for at least 30 s before catheter insertion to maximize the contact time between the antiseptic and skin flora; (III) catheter insertion sites were inspected daily for signs of infection; (IV) manipulation of lines and three-way stopcocks was done with gauze moistened with the same antiseptic used for catheter insertion; (V) blood sampling through the central venous catheter was not allowed; and finally (VI) intravascular catheters were removed if no longer needed, usually before discharge from the ICUs or when a catheter-related infection was suspected.

As such, we should consider the use of chlorhexidine-alcohol as skin antiseptic only as one small part of the full infection control precautions needed before, during, and after intravascular catheter insertion. In addition, there are also other elements that are likely effective in reducing CR-BSI, but were not included in the protocol of this trial, including use of antiseptic or antibiotic impregnated intravascular catheters and use of chlorhexidine-impregnated dressing at the insertion site after catheter insertion (7-9). It is, thus, possible to reduce the incidence of CR-BSI further from 0.7%. Although this study did not demonstrate a significant reduction in length of stay and mortality after using chlorhexidine-alcohol instead of povidone iodine-alcohol as a skin antiseptic before vascular catheter insertion, the results would still suggest that chlorhexidine-alcohol should be used as the routine skin antiseptic for intravascular catheter insertion (with two possible exceptions). The number needed to treat (NNT) to prevent one CR-BSI demonstrated by this study was 250, and the incremental cost to prevent one episode of CR-BSI was only €350 (US$372)—much lower than the widely reported cost associated an episode of CR-BSI (>US$25,000) (3). That said, contact dermatitis as well as anaphylaxis to chlorhexidine have been well described, particularly in neonates and Japanese population, respectively, even when chlorhexidine is applied topically onto skin or mucosa in susceptible individuals (6,8). Thus, clinicians should remain vigilant to monitor patients' response to chlorhexidine either as a topical antiseptic or when chlorhexidine-impregnated catheter is used in hospitalized patients.

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Implications for practice and research

(I) Chlorhexidine-alcohol should be used as a routine skin antiseptic instead of povidone iodine-alcohol before intravascular catheter insertion, with the exceptions in patients who have known or suspected topical or systemic reaction to chlorhexidine.

(II) Chlorhexidine-alcohol skin antiseptic should only be considered as a part of a multimodal approach to prevent CR-BSI. Other elements of infection control precautions are likely more important than the choice of skin antiseptic alone.

(III) Whether using chlorhexidine-alcohol as a skin antiseptic can further reduce CR-BSI when combined with chlorhexidine-impregnated intravascular catheter or chlorhexidine-impregnated dressing at the insertion site remains uncertain, but this merits further investigation.

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Footnote

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What is new for the prevention of catheter-related bloodstream infections?

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Abstract: After the publication in 2011 of latest guidelines of the Centers for Disease Control and Prevention (CDC) for the prevention of catheter-related bloodstream infections (CRBSI) some interesting findings have been published in that field. There has been published that skin disinfection with chlorhexidine alcohol reduced the risk of CRBSI compared to skin disinfection with povidone iodine alcohol, that the implementation of quality improvement interventions reduced the incidence of CRBSI, that the use of chlorhexidine impregnated dressing compared to standard dressings reduced the risk of CRBSI and catheter related cost in an health economic model, and that the use of antimicrobial/antiseptic impregnated catheters reduced the incidence of CRBSI and catheter related cost in clinical studies.

Keywords: Central venous catheter (CVC); bacteremia; prevention; skin disinfection; impregnated catheter; impregnated dressing

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Different measures have been proposed for the prevention of catheter-related bloodstream infections (CRBSI) and have been revised by different scientific societies and the Centers for Disease Control and Prevention (CDC) (1). After the publication of those guidelines in 2011 some interesting articles have been published and could be considered in the prevention of CRBSI.

In this sense, one interesting article has been recently published in September of 2015 by Mimoz *et al.* studying the skin antisepsis (2). In this study were randomized 5,159 catheters to 4 groups of skin disinfection, 2% chlorhexidine and 70% isopropyl alcohol with scrubbing of the skin with detergent before antiseptic application (4% chlorhexidine), 2% chlorhexidine and 70% isopropyl alcohol without scrubbing of the skin with detergent before antiseptic application, 5% povidone iodine and 69% ethanol with detergent before antiseptic application (5% povidone iodine), or 5% povidone iodine and 69% ethanol without detergent before antiseptic application. The authors found that skin disinfection with chlorhexidine alcohol showed a lower risk of CRBSI that skin disinfection with povidone iodine alcohol, with or without scrubbing of the skin with detergent before antiseptic application. Previously, in a study published by Maki *et al.* in 1991 was found that the use of 2% aqueous chlorhexidine decreased the risk of catheter related infection compared to 10% povidone iodine or 70% alcohol (3). In other study by Mimoz *et al.* published in 1996 was found that the use of 0.25% chlorhexidine gluconate plus 0.025% benzalkonium chloride plus 4% benzylic alcohol for skin disinfection compared to 10% povidone iodine reduced the incidence of catheter colonization and catheter related sepsis (4). In a meta-analysis published in 2002 by Chaiyakunapruk *et al.* was found a lower risk of CRBSI with the skin disinfection with chlorhexidine gluconate compared to povidone iodine (5). In a study by Parienti *et al.* published in 2004 was found that the use of 5% povidone iodine in 70% ethanol compared with 10% aqueous povidone iodine for skin disinfection reduced the incidence of catheter colonization (6). In two studies, one published in 2007 and other in 2012, was found that the use of 0.25% chlorhexidine gluconate plus 0.025% benzalkonium chloride plus 4% benzylic alcohol for skin

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disinfection compared to 5% povidone iodine in 70% ethanol reduced significantly the risk of catheter colonization and non-significantly the risk of CRBSI (7,8). Thus, the new key points of the study by Mimoz *et al.* (2) compared with those two previous studies (7,8) were that skin disinfection with chlorhexidine alcohol showed a significantly lower incidence of CRBSI that skin disinfection with povidone iodine alcohol, and that in the chlorhexidine alcohol group were used only two compounds. However, that study by Mimoz *et al.* also has some limitations (2), such as the concentrations of antiseptic agents, and the type and concentrations of alcohol components were different in the different catheter groups. In the guidelines published in 2011 was recommended the use of >0.5% chlorhexidine preparation with alcohol for skin antisepsis (1). That recommendation (with category IA) was based in the findings of the two oldest studies previously commented (3,4). Thus, we think that there is enough evidence to recommend the use of >0.5% chlorhexidine preparation with alcohol for skin antisepsis.

Two other interesting articles has been the meta-analysis by Blot *et al.* (9) and the Spanish experience (10) reporting that the implementation of quality improvement interventions reduced the incidence of CRBSI. In 2014 was published a meta-analysis by Blot *et al.*, which included 41 articles published between 1995 and 2012, reporting a reduction on CRBSI incidence with the implementation of quality improvement intervention for CRBSI prevention (9). In addition, Palomar *et al.* published in 2013 the Spanish Experience in 192 ICUs, and this Bacteremia Zero project decreased the overall median rate of CRBSI from 3.07 to 1.12 infections per 1,000 days of catheter (10). Those quality improvement interventions for CRBSI prevention were different in the different projects and included items as education, training, feedback, clinical reminders, bundle (hand hygiene, chlorhexidine skin antisepsis, maximal sterile barrier precautions, optimal catheter site selection, daily review of line necessity), checklist, empowerment to stop procedure, surveillance, leader designation, prepackaging of central venous catheter (CVC) materials, infrastructure changes, organizational changes. In the guidelines published in 2011 was recommended the use of hospital or collaborative improvement initiatives with the combination of different preventive measures (1). That recommendation (with category IB) was based in different experiences that reported a decrease in the CTBSI incidence after the implementation of those initiatives compared to before practice (11-14). Pronovost *et al.* reported in 2006 a reduction in the median incidence of CRBSI from 2.7 (mean of 7.7) infections per 1,000 days of catheter to 0 (mean, 2.3) after the implementation of the intervention in 103 intensive care units (ICUs) in the Michigan state (13). Thus, we think that there is enough evidence to recommend the implementation of quality improvement interventions; in this sense, we are implementing the Spanish Bacteremia Zero project.

Another two interesting articles have been a RCT by Timsit *et al.* (15) and the meta-analysis published by Safdar (16) reporting a reduction in CRBSI incidence with the use of chlorhexidine impregnated dressing. In the RCT published in 2012 by Timsit *et al.*, which included 4,163 CVC and arterial catheters from critically ill patients, was reported a significant lower incidence of CRBSI with the use of chlorhexidine impregnated dressing compared to standard dressings (15). In a meta-analysis published by Safdar *et al.* in 2014, including 9 RCTs and 11,247 catheters, was found that the use of impregnated dressing reduced the risk of CRBSI (16). In addition, a cost-effectiveness analysis recently published in June of 2015 by Maunoury *et al.* found that antimicrobial chlorhexidine gluconate dressing is more cost-effective that non-antimicrobial transparent dressings using a health economic model (17). In the guidelines published in 2011 was recommended the use of chlorhexidine impregnated dressing if the CRBSI rate has not decreased after implementation of a strategy based in basic preventive measures (which include education, the use of a >0.5% chlorhexidine preparation with alcohol for skin antisepsis, and the use of maximal sterile barrier precautions) (1). That recommendation (with category IB) was based in a meta-analysis (18) and two RCTs (19,20). In the meta-analysis published by Ho *et al.* (18) in 2006, including 5 RCTs and 2,396 catheters (CVC and arterial catheters), was found a significant reduction in catheter colonization and a trend to lower incidence of CRBSI with the use of chlorhexidine impregnated dressing compared to standard dressings (18). In the RCT published in 2009 by Timsit *et al.*, which included 3,778 CVC and arterial catheters from critically ill patients, was reported a significant lower incidence of CRBSI with the use of chlorhexidine impregnated dressing (19). In the RCT published in 2009 by Ruschulte *et al.*, which included CVC and arterial catheters from 631 cancer patients, was reported that the use of chlorhexidine impregnated dressing reduced significantly the incidence of CRBSI (20). Thus, we think that the use of chlorhexidine impregnated dressing could reduce the incidence CRBSI and catheter related costs.

In respect to another measure for the prevention of CRBSI, such the use of antimicrobial/antiseptic impregnated

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catheters, our team has published the efficacy and efficiency of rifampicin-miconazole impregnated catheters and chlorhexidine-silver sulfadiazine (CHSS) impregnated catheters in different clinical circumstances (21-27). Different antimicrobial agents have been used for the impregnation, such as CHSS, rifampicin-minocycline, and rifampicin-miconazole. Veenstra *et al.* published in 1999 a meta-analysis, which included 11 RCTs and 2,603 catheters, reporting that catheters impregnated with CHSS on the external surface (first generation) reduced the risk of CRBSI compared with non-impregnated catheters (28). Later, a meta-analysis published in 2008 by Hockenhull *et al.*, including 3 RCTs and 1,176 patients, reported that catheters impregnated in CHSS on external and internal surfaces (second generation) reduced the CRBSI incidence compared to standard catheters (29). In addition, in a meta-analysis by Falagas *et al.* published in 2007, including 3,452 CVCs from 8 RCTs (using rifampicin-minocycline impregnated catheters in 7 RCTs and rifampicin-miconazole impregnated catheters in 1 RCT), was found a reduction of CRBSI with the use of antimicrobial impregnated catheters compared with non-coated catheters (30). Besides, the use of antimicrobial impregnated catheters has been found to reduce the catheter related cost in some cost-effectiveness analyses (29,31,32). However, in all those cost-effectiveness analyses was included the cost associated with the increase of hospital stay. To simply the cost-effectiveness analyses, our team has carried out several studies to compare the immediate catheter related cost (including only the cost of CVC, diagnosis of CRBSI and antimicrobials for the treatment of CRBSI, and avoiding the cost due to increased hospital stay) using antimicrobial or antiseptic impregnated catheters or standard catheters (22-26). Initially, we found that the use of rifampicin miconazole impregnated catheters could reduce CRBSI incidence and catheter related cost in the jugular venous access with tracheostomy and in the femoral venous access (22,23). Afterwards, we found that the use of second generation of CHSS catheters could reduce CRBSI incidence and catheter related cost in femoral venous access, jugular venous access and subclavian access (24-26). In the guidelines published in 2011 was recommended the use of antimicrobial/antiseptic impregnated catheters (CHSS or rifampicin-minocycline impregnated catheters) if the CRBSI rate has not decreased after implementation of a strategy based in basic preventive measures (which include education, the use of a >0.5% chlorhexidine preparation with alcohol for skin antisepsis, and the use of maximal sterile barrier precautions) (1). This recommendation (with category IA) was based in 3 RCTs showed a reduction on the incidence of catheter tip colonisation with the use of second-generation CHSS-impregnated catheters (33-35) and two RCTs showing that rifampicin-minocycline impregnated catheters reduced the risk of CRBSI (36,37). We think that the use of antimicrobial/antiseptic impregnated catheters could reduce the incidence of CRBSI and catheter related costs.

Conclusions

After the publication in 2011 of latest CDC guidelines for the prevention of CRBSI some interesting findings have been published in that field. There has been published that skin disinfection with chlorhexidine alcohol reduced the risk of CRBSI compared to skin disinfection with povidone iodine alcohol, that the implementation of quality improvement interventions reduced the incidence of CRBSI, that the use of chlorhexidine impregnated dressing compared to standard dressings reduced the risk of CRBSI and catheter related cost in an health economic model, and that the use of antimicrobial/antiseptic impregnated catheters reduced the incidence of CRBSI and catheter related cost in clinical studies.

In our opinion, there is enough scientific evidence to recommend the use of a preparation with >0.5% chlorhexidine alcohol for skin disinfection and the implementation of quality improvement interventions. In addition, the use of chlorhexidine impregnated dressing or antimicrobial/antiseptic impregnated catheters could help in the reduction of CRBSI incidence and catheter related costs.

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Footnote

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Sepsis and Infection

Venous-to-arterial carbon dioxide differences and the microcirculation in sepsis

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Assessment of the microcirculation has been of particular interest in the management of septic shock for over a decade (1,2). It has garnered more attention in light of conflicting data recently on oxygen-derived parameters in patients with sepsis (3). Microcirculatory dysfunction has been linked to organ failure despite adequate macro-hemodynamic stability (4).The microcirculatory perfusion is regulated by the myogenic, metabolic and neurohumoral systems, which in turn affect the arteriolar tone, driving pressure, capillary patency and hemorheology (4). In septic states, perfusion pressure and deformability of cells are reduced, and arteriolar constriction ensues; the end-result is shunting of blood, bypassing essential areas of capillary exchange (5). These changes debilitate the microcirculation and impede tissue oxygenation, resulting in impaired organ functions. Moreover, with stasis in the capillary bed and inflammatory factors released from injured cells that cannot be cleared due to deficient flow, the microcirculation becomes a nidus for continued bacterial growth and persistent insult, sustaining the toxemia and acidemia.

It has been shown that timely aggressive interventions and treatment with early improvements in organ functions increases the probability of survival (6,7). However, improvement in global hemodynamics, such as mean arterial pressures and central venous oxygen saturations ($ScvO_2$) do not always translate to improved perfusion in the microcirculation (8). Assessment of the microcirculation, through indices such as the microvascular flow index, heterogeneity index and proportion of perfused vessels have been found to be lower in septic patients compared to healthy volunteers, with more marked abnormalities among patients with severe sepsis (9). Sophisticated and novel imaging techniques including the sidestream dark-field imaging and nailfold videocapillaroscopy can allow for direct visualization of the microcirculation at the bedside (1). In spite of that, the use of such imaging techniques requires the availability of expertise and special equipment, which may not be readily accessible in the clinical setting and in acute resuscitation. Furthermore, more trials are required to determine the applicability of these modalities in clinical evaluation and in how it can guide resuscitation goals.

More commonly, biochemical tests such as serum lactate concentration and blood gas levels are performed in routine practice as attempts to evaluate the microcirculation. Actual correlation of these parameters with the microcirculation is fraught with numerous confounders (10). The early goal directed therapy by Rivers and colleagues incorporated measurements of $ScvO_2$ as part of the resuscitation goals (7). However, normal $ScvO_2$ may not be a good indicator of adequate tissue oxygenation as low $ScvO_2$ is neither a common nor consistent finding among critically ill patients (11). In addition, $ScvO_2$ levels may not correlate well with the true value of mixed venous oxygen saturation (SvO_2) (12). The potential of measuring CO_2 as a marker of adequacy of resuscitation has been of growing interest in view of its greater solubility in blood compared to O_2 and hence allowing it to diffuse out to the venous effluent despite the low perfusion state from capillary bed shunting (13). An increase in arteriovenous difference in pCO_2 (normal difference less than 6 mmHg) has been found to reliably

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reflect tissue hypoxia (14). Conversely, a lower difference has been associated with a higher cardiac index and better lactate clearance (15-17).

Ospina-Tascón and colleagues performed a study that included 75 patients from a mixed intensive care unit with septic shock to evaluate the adequacy of mixed venous-arterial carbon dioxide difference (Pv-aCO_2) in assessing the microcirculatory perfusion during the early stages of resuscitation (18). Data obtained from a sidestream dark-field imaging device to evaluate the sublingual microcirculatory images was correlated with Pv-aCO_2. The authors found good agreement between changes in Pv-aCO_2 and changes in proportion of perfused vessels (R^2=0.42, P<0.001) at 0 and 6 h (determined by time of pulmonary artery catheter insertion), reflecting the potential of measuring Pv-aCO_2 during resuscitation as a surrogate for adequacy of perfusion in the microcirculation. Apart from the changes in proportion of perfused vessels, changes in Pv-aCO_2 were also significantly associated with changes in functional capillary density and heterogeneity index. Hence, changes in Pv-aCO_2 could potentially provide a good reflection of the state of the tissue perfusion without direct imaging of the microcirculation. Patients with a Pv-aCO_2 of more than 6 mmHg despite a normal ScvO_2 remain inadequately resuscitated and further interventions such as continued fluid resuscitation or inotropes should be considered to improve tissue perfusion (15).

In the study by Ospina-Tascón and colleagues, Pv-aCO_2 did not correlate with cardiac output (R^2=0.01, P=0.45). This finding contrasted with previous experimental models, which showed that Pv-aCO_2 is inversely related to cardiac index (17,19,20). The results of this study support the evidence that Pv-aCO_2 is related to blood flow variations rather than cardiac output alone (21). Nonetheless, knowledge of the cardiac index in septic patients provides clinicians with an idea of the stroke volume index and guides decision making to optimize cardiac function. It is likely that data from Pv-aCO_2 will be complementary to macro-hemodynamic parameters in the global management of patients with septic shock.

The use of mixed venous blood in the study by Ospina-Tascón and colleagues requires blood specimens to be obtained from the mixed venous circulation through a pulmonary artery catheter. The insertion of a pulmonary artery catheter requires expertise, is time-consuming and associated with cardiac complications such as dysrhythmias, valve damage and pulmonary infarction (22,23). It is almost exclusively used in the intensive care units. A study by van Beest and colleagues demonstrated strong agreement between central venous-arterial pCO_2 difference and mixed venous-arterial pCO_2 difference [intraclass coefficient (ICC) =0.70, P<0.001]; likewise an inverse relationship between central venous-arterial pCO_2 and cardiac index (21). However, we are unable to draw any conclusions between the results and the microcirculation due to the post-hoc nature and lack of prospective direct microcirculatory assessment in the study. Nevertheless, the appeal of potentially fewer cardiac complications using a central venous catheter compared with a pulmonary artery catheter coupled with wider generalizability to other areas such as emergency departments should prompt further research in this area (24).

In conclusion, the field of research in microcirculation in septic shock is gaining momentum. The vast majority of research in the management of sepsis has been targeting the macrohemodynamics (7,25-28). Although important, it merely completes one piece of the complicated management jigsaw in sepsis and septic shock. Ospina-Tascón and colleagues have demonstrated very interesting and useful correlations between Pv-aCO_2 and direct assessments of the microcirculation. Though not yet ready for prime time, future research should focus on the microcirculation earlier in the sepsis continuum, even before septic shock develops, and its applicability beyond the walls of the intensive care units.

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Footnote

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Venous-to-arterial CO_2 differences and the quest for bedside point-of-care monitoring to assess the microcirculation during shock

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Provenance: This is a Guest Perspective commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, China).

Abstract: The microcirculation is the anatomical location of perfusion and substrate exchange, and its functional impairment is of paramount importance during the state of shock. The difference in venous-to-arterial carbon dioxide partial pressures (Pv-aCO_2) has recently been reported to correlate with microcirculatory dysfunction during early septic shock with greater fidelity than global hemodynamic parameters. This makes it a potential candidate as a point-of-care test in goal directed therapy that aims to restore microcirculatory function in an emergency clinical context. This early work needs to be explored further, and a better understanding of Pv-aCO_2 during the resuscitation and subsequent patient progression is required. The quest for an ideal bedside point-of-care test for microcirculatory behavior is ongoing, and is likely to consist of a combination of non-invasive sublingual microcirculatory monitoring and biochemical tests that reflect tissue perfusion. These tools have the potential to provide more accurate and clinically relevant data with regards to the microcirculation that more conventional resuscitative monitoring such as blood pressure, cardiac output, and serum lactate.

Keywords: Microcirculation; oxygen; carbon dioxide; sepsis; shock

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Introduction

We read the article "Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock?" (1) with great interest. In their original article, Ospina-Tascón and colleagues test the hypothesis that the difference between mixed-venous and arterial carbon dioxide partial pressures (Pv-aCO_2) may be used as a surrogate marker for the functional adequacy of the microcirculatory flow during septic shock. Such a hypothesis is made in the context of a current understanding that microcirculatory behavior is more predictive of outcomes following septic shock than the more conventional global hemodynamic parameters such as mean arterial pressure and cardiac index (2). At present it may be relatively simpler to collect blood samples and calculate the Pv-aCO_2 than to undertake bedside monitoring of the microcirculation (especially in an emergency scenario). Pv-aCO_2 results are also more immediate than many other methods of monitoring the microcirculation, such as sidestream dark field (SDF) videomicroscopy, which currently requires lengthy offline analysis to produce results. This means that the authors' research question has far-reaching implications for those interested in monitoring microcirculatory behavior in real-time during shock.

The authors tested their hypothesis by comparing standard microcirculatory parameters (3) taken from bedside sublingual SDF imaging with Pv-aCO_2 measurements at

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the same two time points (at PAC placement—average of 3 h after first hypotensive episode—and then at 6 h subsequently). This study was conducted prospectively over 15 months at a relatively large South American University Hospital intensive care unit (ICU), and included 75 patients with septic shock who had a pulmonary artery catheter (PAC) placed for hemodynamic monitoring. The authors divided the patients into three predefined Pv-aCO_2 categories for analysis (<6.0, 6.0–9.9, and ≥10 mmHg), a decision they attribute to previous observations (4). Their findings elegantly demonstrate that Pv-aCO_2 is strongly associated with microcirculatory function but poorly associated with systemic hemodynamic variables such as mean arterial pressure and cardiac output. Such findings are in keeping with the current concept that microcirculatory parameters are more predictive of tissue oxygenation in a shock state than traditional global parameters (5-7).

Point-of-care is the future: but how?

Part of the rationale for Ospina-Tascón and colleagues' work is the quest to find a simple and effective way of monitoring the microcirculation without having to use traditional bedside monitoring devices such as sublingual SDF, or the newer incident dark field (IDF) imaging (8). This is particularly important because despite recent technological advances, SDF or IDF videomicroscopy are not yet capable of producing immediate objective microcirculatory measurements at the bedside. Instead, the clinician must take the video clips away and meticulously grade them for quality, before using specialized computer software to laboriously and systematically extract the desired parameters from the images. Indeed some video clips may be discarded completely if their quality assessment is not satisfactory. Such a process can be lengthy, and also takes place away from the patient in place and time. Mainstream reporting of microcirculatory parameters are therefore currently confined to research rather than in the clinical capacity. In their argument Ospina-Tascón and colleagues cite a review article written by the senior author (9) which advocates a future in which a goal directed approach to resuscitation may be guided by bedside monitoring, but that none yet exists. In their article, they propose that perhaps Pv-aCO_2 may have a place in the tracking of microcirculatory flow during shock.

We believe that optimism is warranted when it comes to the future of point-of-care microcirculatory monitoring. Recent international efforts have demonstrated that there is good inter-rater reliability and diagnostic accuracy between subjective evaluation and offline analysis of microcirculatory parameters (10). Furthermore real-time qualitative assessment of the microcirculation at the bedside is feasible, and compares well to offline analysis (11). It is therefore feasible (and perhaps even highly likely) that in the near future bedside microcirculatory monitoring may allow for real-time assessment of the microcirculation by trained clinicians either in a continuous manner, or at any desired time-points. Although we agree that Pv-aCO_2 is likely to be a useful adjunct to the understanding of the greater clinical picture, traditional microcirculatory monitoring techniques have an advantage in that the can characterize flow, density, and heterogeneity, giving a greater breadth of targets for goal directed therapy. A disadvantage of Pv-aCO_2 as presented by Ospina-Tascón and colleagues is that it is only defined in three categories: a trichotomy of 'normal', 'abnormal', and 'even worse', which may limit may its clinical and diagnostic utility. Furthermore although the cut-off between 'normal' and 'abnormal' may be considered as 6 mmHg (12), the justification for the higher threshold of 10 mmHg for the worst group is uncertain and is not mentioned in the earlier work they cite (4). We agree with the authors' acknowledgement that if Pv-aCO_2 is to be used in the manner suggested then it would require more detailed examination and validation.

Risks and benefits

Although the drawing of blood may seem less invasive and time consuming than sublingual microcirculation monitoring, a pulmonary artery catheter is still required to obtain these mixed samples, and is not without its own complications (13-15). Conversely there have been no reports of complications from sublingual microcirculation monitoring. Furthermore in modern intensive care practice it is unusual to place PAC catheters purely for systemic hemodynamic monitoring in septic shock. Ideally if such blood tests are to be recommended in the monitoring of microcirculatory behavior, they ought to be readily available with minimal risk of complication. If clinical team decides that there is no indication for a PAC then a risk/benefit analysis may perhaps not be deemed favorable for the monitoring of Sv-aCO_2 outside the context of an ethically approved clinical trial.

Central venous CO_2 saturation ($ScvCO_2$) samples may be obtained from a more commonly placed central venous catheter, and may be just as useful in some circumstances as pulmonary artery samples ($SvCO_2$) (16). However, although

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the utility of $ScvO_2$ was initially considered to be promising for early goal directed therapy (17), such an approach to resuscitation did not seem to be effective in later studies such as the ProCESS trial (18), ARISE study (19), and ProMISe trial (20). Ospina-Tascón and colleagues report that Pv-aCO_2 is more sensitive than $ScvO_2$ in detecting microcirculatory derangement, and we agree that further investigation is required. Given the experience with $ScvO_2$, caution should be taken in positioning Pv-aCO_2 as the 'new candidate' in the field of tissue perfusion and a potential target for goal directed therapy.

Limitations of a 'snapshot' approach

Values for Pv-aCO_2 at particular time-points may also be limited in utility by their 'snapshot' nature. In order to track the clinical progress of a patient or microcirculatory reaction to particular interventions, repeated blood draws might be required. Furthermore the clinician must decide at which time-points this is best suited. Ospina-Tascón and colleagues have used the arbitrary T0 and T6 time-points, and further evidence is required before these can be considered relevant to clinical practice. This is particularly important when they report a length of stay in the ICU of 6 (interquartile range, 2–10) days. Further work is required to determine the utility of Pv-aCO_2 in detecting and following changes in the microcirculation during the patient's clinical progression. For example it would be interesting to discover what happens to the Pv-aCO_2 beyond the 6-h time point, and whether it 'normalizes' at the same rate as the microcirculation in patients who make a good recovery. Conversely, does it persist, or deviate from the behavior of the microcirculation, and if so, in what manner?

Sublingual microcirculatory monitoring may offer an opportunity for continuous monitoring, as well as monitoring at the time of an intervention, and at regular intervals, without requiring patient's blood. Previous work has demonstrated the feasibility of repeated measurements at short intervals before, during, and after interventions (21,22). We believe that a combined approach may offer the best information to the clinician managing shock in the future by (I) examining the physical behavior of the microcirculation using point-of-care monitoring, and (II) comparing these parameters to the chemical behavior of the microcirculation by means of carbon dioxide partial pressures. Such an approach may be a more sophisticated version of the older, more conventional blood pressure and serum lactate monitoring during resuscitation in common practice.

Other forms of shock?

Of further interest to our group, would be whether the findings of Ospina-Tascón and colleagues can be repeated in the context of hemorrhagic as well as septic shock. These entities are different in many ways, but recent clinical work has shown that similarly dysfunctional microcirculatory behavior may be present following traumatic hemorrhagic shock (23). The ongoing MICROSHOCK study (ClinicalTrials.gov ID: NCT02111109) is also examining immediate microcirculatory derangement after injury and hemorrhagic shock using sublingual IDF technology, but results are not yet available. Of note, the CO_2 gap is also being recorded for these patients, and would provide information with regards to the effects of hemorrhagic shock rather than septic shock. It seems that regardless of the cause of shock, there is a trend towards a greater understanding of the microcirculatory behavior, and a desire for point-of-care, bedside technology in order to direct resuscitation and improve outcomes for patients with these serious pathologies.

Conclusions

The difference between mixed-venous and arterial carbon dioxide partial pressures appears to reflect changes in microcirculatory function and has the potential to make an impact in the search for clinically relevant target for goal directed therapy. Caution and further investigation are both warranted if this is to be translated into clinical practice. Combined with advances in non-invasive sublingual microcirculatory monitoring, point-of-care, bedside, physical and chemical monitoring of the microcirculation may provide a new paradigm for the targeted resuscitation of patients in shock.

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Footnote

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Choice of crystalloids in sepsis: a conundrum waiting to be solved

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One of the mainstays of sepsis and septic shock management is early intravenous fluid resuscitation to correct intravascular hypovolemia and restore adequate perfusion (1). There is an ongoing controversy on the optimal volume and choice of intravenous fluids to be administered (2,3). Recent systematic reviews and meta-analyses have concluded that pentastarch and hydroxyethyl starch are inferior to crystalloids as starch solutions increase the risk of kidney injury and death in patients with sepsis (4,5). Non-synthetic colloids such as albumin demonstrated no additional measurable harm or benefit when compared to crystalloids in sepsis (6,7). While the debate on crystalloids *vs.* non-synthetic colloids continues, another deliberation regarding the choice of crystalloids; 'balanced' *vs.* 'non-balanced', has started to garner interest.

Saline (0.9% NaCl solution), also widely known as 'normal' saline or 'physiological' saline is by far the most commonly used intravenous solution in the world with over 200 million liters sold annually in the United States alone (8). Over 1 million liters of intravenous saline are administered to patients worldwide daily (9). Paradoxically, normal saline has been identified as neither normal nor physiological in an editorial way back in 1970 (10). It is considered 'non-balanced' due to its supra-physiological concentration of chloride ions (*Table 1*). Liberal administration of saline has been shown to result in hyperchloremia and metabolic acidosis (11,12). Hyperchloremia is postulated to mediate vascular smooth muscle contraction, which potentiates norepinephrine and angiotensin II-induced vasoconstriction thus reducing renal blood flood via tubulo-glomerular feedback (13,14). In addition, excessive salt administration causes decreased diuresis, fluid overload and interstitial edema leading to further reduction in renal blood flow (15). Both mechanisms exacerbate the risk of pre-renal kidney injury. The hyperchloremic metabolic acidosis may also have deleterious effects on the immune system that is demonstrated by increased plasma nitric oxide levels and pro-inflammatory cytokines (16).

The search for the ideal fluid for resuscitative use, which should best resemble constituents of human plasma, has led to the development of 'balanced' solutions that have minimal effect on the acid-base equilibrium, or with a physiological or low content of chloride. Examples of such solutions include Ringer's lactate, Hartmann's solution, Plama-Lyte and Sterofundin (*Table 1*). Many have jumped on the recent bandwagon to reduce the use of chloride-rich solutions in favour of balanced solutions. The current clinical evidence for the use of balanced solutions, particularly in sepsis and septic shock is largely drawn from observational studies involving patients with sepsis, septic shock or systemic inflammatory response syndrome (17,18). Other observational studies from intensive care units have also demonstrated decreased risk of acute kidney injury in patients receiving balanced solutions compared to saline (19-21). However, mixtures of intravenous fluids are frequently used in clinical practice, and it is unclear if morbidity and mortality are influenced by different mixtures of fluids.

A study by Raghunathan and colleagues published in 2015 sought to test the hypothesis that specific mixtures of intravenous fluids during initial resuscitation in patients with sepsis are associated with outcomes such as mortality, length of hospital stay and cost (22). This retrospective cohort study included 60,734 patients with sepsis over 5 years (from 2006 to 2010) from 360 intensive care units across the United

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Table 1 Composition of plasma and commonly-used crystalloids

Fluid	Osmolality (mOsm/kg)	Osmolarity (mOsm/L)	Na^+	Cl^-	K^+	Ca^{2+}	Mg^{2+}	Buffer
Plasma	288	291	142	103	4.5	2.5	1.25	24[†]
0.9% saline	286	308	154	154	0	0	0	0
Ringer's lactate	254	273	130	109	4	2.7	0	28[‡]
Hartmann's solution	257	276	131	111	5	2	0	29[‡]
Plasma-Lyte 148	Unknown	295	140	98	5	0	1.5	50[§]

Concentration of constituents in mmol/L. [†], bicarbonate; [‡], lactate; [§], acetate (27 mmol/L) and gluconate (23 mmol/L).

States. Four mutually exclusive categories were compared with one another: (I) patients who received saline exclusively; (II) patients who received saline and balanced crystalloid solutions; (III) patients who received saline and colloids (either hydroxyethyl starch or albumin); and (IV) patients who received all three types of fluids. After inverse probability weighting-based adjustment, patients who received saline and balanced solutions had the lowest in-hospital mortality of 17.7%. The effects were maintained even after hierarchical logistic regression modelling and pairwise propensity score matching on day 2 of hospitalization. They also showed that treatment with colloids resulted in increased mortality when balanced crystalloids were not coadministered and no difference in survival when balanced crystalloids were coadministered. Therefore, the authors surmised that the distinction between types of crystalloids used were more significant than the crystalloid *vs.* colloid differentiation.

The results of this study by Raghunathan and colleagues seem to back up previous systematic reviews on the deleterious effects specifically of synthetic colloids from previous systematic reviews and meta-analyses (4,5). The main drawback of this study is its retrospective nature, though the authors have commendably gone through great lengths using statistical methods to control for confounding. Another limitation is the use of administrative and financial data rather than actual chart reviews. Furthermore, only 9.2% of those meeting the inclusion criteria were finally analysed after various exclusion criteria were applied and only included vasopressor-dependent sepsis, further limiting its generalizability (22). Nevertheless, this study is currently the only one that tried to examine pragmatically how real-world use of mixtures of fluids is associated with clinically important outcomes. It is likely that the practice of using different solutions at different times is prevalent worldwide. Despite its shortcomings, the results of this study may shed some light into the effects of various combinations of intravenous fluids in critically ill patients.

The benefits of balanced solutions have also been demonstrated in other clinical scenarios where the patients required large amounts of intravenous fluids. In perioperative care, the administration of balanced solutions to adult and pediatric patients in surgery was shown to be associated with less metabolic derangement, in particular hyperchloremia and metabolic acidosis (23). Similar associations were also demonstrated in patients who suffered acute severe traumatic injuries requiring fluid and blood transfusion (24). In patients requiring major open abdominal surgery, treatment with balanced solutions was associated with fewer complications, namely postoperative infection, renal failure requiring dialysis, blood transfusion, electrolyte disturbance, acidosis investigation and intervention (8).

The maelstrom concerning the use of saline mainly centers on its chloride content. The possibility of hypernatremia and its association with adverse outcomes has not been addressed in detail (25). Of note are the differences in osmolarity and osmolality between saline and balanced solutions (*Table 1*) (26). The values of osmolarity and osmolality are interchangeable in dilute physiological solutions. However, incomplete ionization of the solutes in balanced solutions like Ringer's lactate and Hartmann's solution renders them hypotonic compared to normal plasma *in vivo* (27). A study on human volunteers showed that infusion of large volumes of Ringer's lactate decreased serum osmolality and shorter time to first urine output (28). It was postulated that the inhibition of release of antidiuretic hormone resulted in this finding. Such disparity needs to be considered from a mechanistic perspective in future studies.

While the presence of hyperchloremic acidosis is irrefutable in saline infusion, the degree of adverse effects is directly related to the amount of fluid administered (29). Correction of hyperchloremic acidosis alone is unlikely to lead to substantial clinical benefits as it has been considered inconsequential, resolving within a day if appropriate

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amounts of saline are administered (30). The lack of potassium in saline solution may be viewed as an advantage in some conditions such as renal failure where risk of hyperkalemia is relatively higher. The use saline infusion in other conditions such as diabetic ketoacidosis and traumatic brain injury is currently still a subject to considerable disagreement.

The only randomized trial done thus far to compare saline *vs*. balanced solutions in intensive care units was recently published (31). Plasma-Lyte 148 was compared to saline in a multi-center, cluster-randomized, double-crossover study that failed to demonstrate any difference in risk of acute kidney injury [relative risk (RR), 1.04; 95% confidence interval (CI), 0.80–1.36], requirements of renal replacement therapy (RR, 0.96; 95% CI, 0.62–1.50) and mortality (RR, 0.88; 95% CI, 0.67–1.17) at 90 days in 2,092 patients in the intensive care unit. Although the trial is of a superior design compared to previous observational studies, the study population consisted of mainly non-septic surgical patients who had a low overall incidence of acute kidney injury (9.4%) and mortality (8.0%). The very small subgroup analysis of patients with sepsis (n=77) demonstrated a higher incidence of acute kidney injury (20.8%) and mortality (15.5%). Thus, the treatment effect of balanced solutions in this low-risk group may be underestimated.

In conclusion, based on current, predominantly observational evidence, it is justifiable to consider balanced solutions as the first choice crystalloids for resuscitation of septic patients. The solution (pun intended) to the conundrum of which is the ideal crystalloid to use in sepsis is far from close. Further multicenter randomized trials including medium to high risk septic patients are required to arrive at more robust conclusions and provide more concrete recommendations.

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Footnote

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Preventing the development of acute cor pulmonale in patients with acute respiratory distress syndrome: the first step

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Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by acute hypoxemic respiratory failure that is associated with substantial mortality even 40 years since it was first described. Although hypoxemia appears to be the most conspicuous abnormality noticed with this condition, it isn't the most common cause of death. Conservative oxygen saturation targets of 88–92% have been recently reported to be as effective as targeting saturation above 96%, which indicates that the human body can survive relatively short periods of relative hypoxemia without any lingering effects (1). On the other hand, circulatory failure is frequently encountered and is reported to be one of the major causes of mortality (2). Systemic inflammation drives the shock state to a large extent. Nevertheless, another significant cause of circulatory failure is pulmonary vascular dysfunction and elevated pulmonary vascular resistance that is frequently observed in ARDS. These subsequently lead to failure of the right ventricle and refractory cardiogenic shock in addition to a component of distributive shock state which often coexists. Although hypothesized and agreed upon by many, the direct effect of pulmonary vascular dysfunction on mortality in ARDS has been difficult to demonstrate. Utilizing transesophageal echocardiogram probes (TEE), the demonstration of severe forms of right ventricular dysfunction and acute cor pulmonale (ACP) is relatively easier compared to quantifying pulmonary vascular dysfunction, which requires the use of a pulmonary artery catheter (PAC). Modern intensive care units around the world report the existence of right ventricular dysfunction in about 25–50% of patients with severe ARDS (3). Despite these numbers, current ARDS guidelines do not recommend searching for evidence of ACP or strategies directed at treating elevated right ventricular pressures as a part of managing ARDS. This is probably because of lack of any high quality evidence that clearly demonstrates the effect of ACP on mortality in ARDS.

Several recent studies have demonstrated strategies that have improved survival rates in ARDS (4-6). Most of these involve advancements in ventilator strategies and measures to protect the lung while attempting to improve oxygenation. However, the pooled mortality rate in ARDS still stands at 40% in spite of best standards of care (7). This invites the question "Is there something else that can be offered to improve mortality in ARDS? Could the early identification and management of ACP associated with ARDS help us save more lives (8)?" Unfortunately, the answer is not entirely clear with the evidence available to us.

As pointed out earlier, although the prevalence of ACP resulting from pulmonary vascular dysfunction has diminished with safer and more effective strategies of mechanical ventilation, it continues to occur in 25–50% of patients with ARDS (3,9-15). Pulmonary vascular dysfunction is a result of acute vascular inflammation that spills over from the alveoli to the microcirculation leading to vessel edema, thrombi as well as vascular remodeling that invariably follows any vascular insult (16). Part of this increased pulmonary vascular pressures may be a result of the way we chose to ventilate our patients. Positive end expiratory pressure (PEEP) has been proven to help oxygenation by keeping diseased alveoli open, thus

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improving gas exchange and preventing atelectrauma. Unfortunately, it also creates heterogeneity within the lung architecture—some collapsed alveoli because of alveolar filling from ARDS and other relatively normal areas of the lung that become hyper-expanded as a result of high levels of the PEEP used to keep oxygenation at a level to sustain life. These areas with overstretched alveoli have compressed vessels in the alveolar septa with increase in vascular resistance that leads to the development of pulmonary hypertension (17). On the other end of the spectrum are those areas of the lung with collapsed alveoli. These areas also have high vascular resistance. This results from the loss of radial stretch on the blood vessels resulting in smaller vessel diameters leading to increased vascular resistance. This follows Poiseuille's equation which describes the resistance to be inversely proportional to the radius to the fourth power. Regional hypoxic vasoconstriction in these atelectatic areas also plays a part in increasing vascular resistance. Finally, hypercapnia ($PaCO_2$>60 mm of Hg) has been described to contribute to elevated pulmonary arterial pressures and ACP (14). It is difficult to objectively demonstrate pulmonary vascular dysfunction due to fact that most modern intensive care units have shied away from using pulmonary catheters. In one of the few studies that looked at pulmonary vascular dysfunction in ARDS, Bull *et al*. (18) reported a greater than 70% incidence of pulmonary vascular dysfunction among those with acute lung injury. Right ventricular dysfunction and ACP occurs as downstream effects of pulmonary vascular dysfunction and elevation in pulmonary vascular resistance. The study by Mekontso Dessap *et al*. (19) adds to the growing literature providing evidence to suggest that ACP is common among those with moderate-to-severe ARDS and that it persists even after the implementation of low tidal volume ventilation strategies.

Granted that we do not have clear evidence to prove that ACP affects survival in ARDS, there is sufficient evidence to suggest that it negatively affects the course of the disease. The following studies have investigated the independent effects of ACP on morbidity and mortality. Lheretier *et al*. had demonstrated that patients with ACP required higher levels of inhaled nitric oxide and required proning more often than those without ACP (15). Boissier *et al*. reported statistically significant higher 28-day mortality in those with ACP of 67% (14). Bull *et al*. published data on 470 patients with ARDS demonstrating an increased 60-day mortality with elevated baseline transpulmonary gradient (TPG) >12 mm of Hg. Both pulmonary vascular resistance index and TPG were determined to be independent risk factors for increased 60-day mortality, number of ICU free days, ventilator free days on multivariate analysis in his study (18).

What does Mekontso Desapp's study add to the current literature?

Mekontso Dessap and colleagues present a retrospective analysis in *Intensive Care Medicine* proposing a risk prediction model to identify those at high risk of developing ACP (19). The authors added 250 new patients to a previously existing dataset to create one of the largest collections of patients (752 patients) with moderate to severe ARDS with focus on the development of ACP and to further characterize the factors predicting its development. They report a 22% prevalence rate of ACP when TEE was performed within 3 days from the diagnosis of ARDS. All patients included in this study were managed with low tidal volume ventilation strategy and plateau pressure were kept below 30 mmHg. The authors defined ACP using a TEE probe that was placed in the mid-esophagus and measured the end diastolic left and right ventricular area (LVEDA and RVEDA). They also looked for evidence of septal dyskinesia at end systole from the transgastric view. The authors defined ACP by a RVEDA/LVEDA ratio greater than 0.6. A cutoff of 1.0 or more was taken to be a marker of severe ACP (7.2% of patients).

The authors identified four variables that stood out as statistically significant predictors of ACP—pneumonia as a cause of ARDS, driving pressure of >18 cm H_2O, PaO_2/FiO_2 <150 mmHg and $PaCO_2$ >48 mmHg. These variables were first recognized among 502 patients (called the derivation cohort) and then applied to 250 patients (the validation cohort) confirming their soundness. The authors then used these variables to construct a risk score prediction model for the development of ACP. The prevalence of ACP is approximately 20% when two variables are present and more than 30% when three are present. It goes up to a 75% when all four criteria are met. Based on these results, the authors recommend utilizing TEE to look for evidence of ACP when the risk score is 2 or more. Although the authors report a marginally higher mortality in those with ACP than those without (48% *vs*. 44%; *P*=0.17), statistically significantly higher mortality was noted only in those patients with severe ACP compared to the rest (57% *vs*. 42%; *P*=0.03).

In summary:

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(I) Even with targeted low plateau pressures below 30 mmHg, there is a high incidence of ACP among patients with severe ARDS.
(II) Defined four variables whose presence could predict the development of ACP:
  (i) pneumonia as a cause of ARDS;
  (ii) driving pressure of >18 cm H_2O;
  (iii) PaO_2/FiO_2 <150 mmHg;
  (iv) $PaCO_2$ >48 mmHg.
(III) Suggested searching for evidence of ACP with a TEE when the risk score is greater than 2 among patients with ARDS.
(IV) Mortality was found to be significantly higher in those patients with severe ACP (57% *vs.* 42%).

The question that naturally stems from the results of the study is what would be the next step once we diagnose the existence of ACP? Unfortunately, we do not have evidence to suggest that any therapy targeted towards the management of ACP will actually improve outcomes in ARDS. Hence, it is often left to the institutional intensive care practices to determine management strategies on a case-by-case basis. What we know for sure is that mortality is high once the patient develops ACP (48%) (19). Thus, practices that are known to protect the right ventricle and reduce right ventricular pressures are likely to reduce mortality if applied at the right time and in the right fashion. This study (19) provides evidence to suggest that the same measures that are known to limit lung stretch and damage in ARDS—such as limiting driving pressures to the lower end (20), proning patients with a PaO_2/FiO_2 ratio <150 particularly those with two or more predictors of ACP (4), and preventing the partial pressure of CO_2 to climb above 48 mmHg will decrease the incidence of ACP and subsequent risk of circulatory dysfunction (15). Targeting plateau pressures below 30 cm of H_2O is accepted to be lung-protective based on the results of the ARDSNet results, albeit it still exposes the right heart to considerable strain when plateau pressures are above 28 cm of H_2O (21). Accordingly, it might not be unreasonable to target lower plateau pressures. It is debatable whether one should attempt to treat elevated CO_2 levels by extracorporeal removal. A lack of survival benefit utilizing this modality of treatment limits its applicability in patients with ARDS (22-24). It is important to recognize that none of the studies using extracorporeal CO_2 removal focused on patients with ACP. Prone positioning is also known to help hemodynamics by unloading the right ventricle and hence reduce right ventricular dilatation. This effect is most obvious in patients who have both severe ARDS and ACP (10). Improvements in LVEF are also noted with proning, which might contribute to the improvement in hemodynamics seen with this maneuver (10).

A concept of RV protective ventilation (25) has been proposed to encounter the high risk of ACP in severe ARDS which could be applied to those patients who carry at least two of the high risk determinants as described by the Mekontso Dessap (19). This concept applies those measures known to reduce the chances of developing ACP as described above. PEEP is applied being cognizant of its deleterious effects on the RV (26).

Whether these measures will be effective in improving the survival in severe ARDS is a question for which there are no clear answers. The lack of a clear relationship between ACP and survival stems from the fact that such patient being sicker get the most aggressive treatment including proning which by itself is known to unload the right ventricle and improve right ventricular function (27). It would be unethical to hold treatment from such patients to form a control arm for such a hypothetical study. Having said that, the results of this current study by Mekontso Desapp *et al.* (19) indicates that a severe ACP increases mortality. These results should encourage intensivists to utilize right ventricular protective ventilatory strategies described above to prevent the development of severe ACP. However, whether applying the same principles of treatment after severe ACP has already set in would change outcomes is anybody's guess.

To conclude, it is probably premature to consider the results of this study as definitive proof of a cause-effect relationship between ACP and mortality, but it does indicate that severe ACP increases mortality. Recognition of the four-point clinical variables can help identify those at a high risk of developing ACP. Application of these variables may help us select the right patient for the most aggressive therapy with specific attention given to the state of the right ventricle in order to avoid consequences of hemodynamic compromise resulting from a failing right ventricle.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Editorial on low-dose acetylsalicylic acid treatment and impact on short-term mortality in *Staphylococcus aureus* bloodstream infection: a propensity score-matched cohort study

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Provenance: This is a Guest Editorial commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).

Abstract: The manuscript "Low-Dose Acetylsalicylic Acid Treatment and Impact on Short-Term Mortality in *Staphylococcus aureus* (*S. aureus*) Bloodstream Infection: A propensity Score-Matched Cohort Study" published in *Critical Care Medicine* by Osthoff *et al.* reported an association of aspirin intake with a reduced short-term mortality. Direct anti-microbial effects of aspirin and its metabolite salicylate were suggested in preclinical studies. Especially intriguing is the inclusion of a control group with *Escherichia coli* (*E. coli*) blood stream infections in this study, in which aspirin was not associated with an improved outcome. However, as other observational studies also reported benefits of aspirin in critically ill patients, randomized trials are needed to confirm the effects of low-dose aspirin.

Keywords: Aspirin; *Staphylococcus aureus* (*S. aureus*); mortality; *Escherichia coli* (*E. coli*)

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Acetylsalicylic acid (ASA) at low doses is usually regarded as an anti-platelet substance. The mode of action is an irreversible inhibition of the enzyme cyclooxygenase (COX) by acetylation (1,2), which inhibits arachidonic acid induced platelet aggregation even after single oral doses of 162 mg of aspirin (3). This effect is limited to COX-1 within platelets at low doses. At higher doses ASA also inhibits COX-2, which explains its use as an anti-inflammatory and analgetic drug. The use of low-dose ASA in the prevention of thromboembolic events has remained essential up to now (4,5).

However, apart from these well-known effects other beneficial responses were assigned to ASA and subject to investigation. ASA-triggered lipoxins, like other lipid mediators regulated by prostaglandins and COX enzymes, are thought to play an important part in the resolution of inflammation (6,7). Interestingly, at higher doses ASA inhibits the NF-κB pathway (8).

Inhibition of platelets, nowadays identified as "immune" cells contributing to inflammation activation and regulation, may prove beneficial in severe systemic inflammatory responses as inhibition may reduce the platelets' contribution to such a disease state (8,9). Various observational studies were performed showing overall positive effects of low-dose ASA in community-acquired pneumonia, in critically ill patients or in acute respiratory distress syndrome (10-14). Moreover, a possible role of low-dose ASA in prevention of cancer was suggested (15).

Finally, ASA was demonstrated to exert direct, antimicrobial effects. In a rabbit model of *Staphylococcus aureus* (*S. aureus*) endocarditis ASA at 8 mg/kg/day reduced vegetation weight, growth, bacterial density and embolic lesions (16). These observed benefits were at least partially diminished when other doses (4 and 12 mg/kg) were used. It's important to note that salicylate levels at the dose of 8 mg/kg were ranging between 47 and 53 μg/mL over a period of 12 hours, which is much higher than peak levels measured

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in healthy volunteers after a single dose of 162 mg of ASA, which were approximately 7.6±1.4 μg/mL (3). After intake of 800 mg of different NO-aspirin formulations mean peak plasma levels ranged between 10 and 21 μg/mL (17). Considering these data from healthy volunteers, rather high doses of aspirin would be necessary to achieve the proposed doses. On the other hand, the interspecies differences have to be considered. Beneficial effects of ASA in combination with ticlopidine were also found in a rat endocarditis model caused by *Enterococcus faecalis* and *Streptococcus gallolyticus* (18). Salicylic acid, the main metabolite of ASA, affected the virulence of *S. aureus in-vitro* by activating a stress response regulon *sigma factor β.* This stress response *reduces α-hemolysin* (*hla*) and *fibronectin-binding protein A* (*fnbA*) gene expression (19,20). These results were confirmed in a study investigating not just the adhesive potential of *S. aureus* but also its invasiveness using human vascular endothelial cells. ASA reduced the virulence of *S. aureus* in this *in vitro* model (21). Again doses of 30 and 50 μg/mL were used. However, using a distinct, encapsulated *S. aureus* strain, ASA enhanced invasiveness in an *in vitro* model using bovine mammarian endothelial cells (MAC-T) (22). This suggests that the effects of ASA may differ between strains of *S. aureus* and more data are needed to better define the antimicrobial effects of ASA (22). Interestingly platelets were demonstrated to contribute to biofilm formation and inhibition of platelets by low-dose ASA may reduce biofilm formation and its resistance to antimicrobial substances (23).

In their manuscript Osthoff *et al.* investigated effects of low-dose ASA in *S. aureus* bloodstream infection (BSI) (24). Low-dose ASA was associated with a reduced mortality in this propensity score-matched cohort study. Of note, beside ASA intake another difference was evident between groups: in the ASA group significantly more patients were treated with statins compared to the non-ASA group. The intake of statins alongside the intake of low-dose ASA is not merely surprising taking the overlapping indications into account. Although statins were associated with reductions in mortality in other non-interventional studies (25), in the multivariate analysis of this study statins were not associated with an improved clinical outcome. Thus, although it cannot entirely be excluded, statin use should not interfere with the study's endpoints.

How should the findings of the study be interpreted and integrated into the growing body of evidence that there may be more to ASA than inhibiting platelet aggregation? This retrospective study was well-designed with a large propensity score-matched cohort, groups were well-balanced, except for the statin use, and existing standard practices for treatment and diagnosis of BSI within the hospital improve the quality of data. There is one particular strength, which adds much to the validity of the results: the inclusion of the *Escherichia coli* (*E. coli*) BSI control group. Thus, it is tempting to assume that direct antimicrobial effects of ASA against *S. aureus* cause this benefit. Furthermore it suggests that platelet inhibition in BSI caused by *E. coli* does not improve survival. After all, it has to be emphasized that although this study certainly adds important information still many questions remain. Observational studies, no matter how well designed and performed, are prone to bias and confounders. To confirm the reported, potentially beneficial effects of treating patients with *S. aureus* BSI with low-dose ASA, or other reported positive effects of ASA in critical illness, randomized trials are necessary. As the number of observational studies suggesting positive effects of ASA increase the call for such studies becomes louder. It seems likely that realization of such a trial is subject to academic research, as ASA use does not offer enough financial incentives for industrial sponsoring. Until randomized trials are performed, it remains unknown whether the observed effects are true or subject to bias.

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Footnote

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Continuous or interrupted chest compressions for EMS-performed cardiopulmonary resuscitation

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High-quality cardiopulmonary resuscitation (CPR), which can supply blood to critical organs such as the heart, lungs, and brain, with an optimal level of perfusion pressure, is known to be essential for the return of spontaneous circulation (ROSC) and a good outcome in case of out-of-hospital arrests (OHCAs) (1,2). The CPR guidelines 2000 (3) recommended the use of ventilation for OHCA victims with a small tidal volume and low inspiratory pressure to avoid gastric inflation. These guidelines also recommended chest compression (CC) at a rate of 100 compressions per minute with a complete release of pressure after each CC to achieve optimal forward blood flow.

Since the publishing of the CPR guidelines 2000, increasing attention has been dedicated to the proportion of time spent performing or interrupting CCs. Coronary perfusion pressure is an important indicator pertaining to the ROSC (4,5). It has been reported that a desirable level of pressure is obtained only after CCs are continued for a longer period, and the level decreases rapidly after CCs are discontinued (6). In the revised CPR guidelines of 2005 (7,8) in Europe, the US, etc., the interruption of CCs was minimized to further improve the quality of CPR. A change in the compression to ventilation ratios from 15:2 to 30:2 and the initiation of CCs immediately after defibrillation were also introduced. Furthermore, to reduce the interruption of CCs by rhythm analysis with an automated external defibrillator (AED), defibrillation was delivered only once after a 2-min interval of rhythm analysis (known as the "1-shock strategy"). Moreover, the time taken to rescue breathing (inspiration) was reduced from 2 to 1 sec. For advanced life support, CCs at a rate of 100 per minute, with ventilations at a rate of 10 per minute without pauses, were applauded for patients who had been fitted with an advanced airway.

Many observational studies have reported that higher survival rates are often associated with a higher, and not lower, CC fraction (CCF) in patients with cardiac arrest and a shockable initial rhythm (9-12). A prospective cohort study showed that increased CCF among non-VF OHCA patients was associated with a trend toward an increased likelihood of ROSC (13).

In the December 3, 2015, issue of *NEJM*, the resuscitation outcomes consortium (ROC) in the US reported a trial comparing continuous and interrupted CCs during CPR performed by emergency medical service (EMS) personnel (14). A notable difference between this ROC report and earlier trials was the application of the CPR-process monitoring. Committee members periodically reviewed data and assessed whether prescribed targets for performance were met for measures such as enrollment rate, treatment-adherence rate, and key elements of concurrent care. The committee also made recommendations regarding steps to be implemented to increase the rates.

In this cluster-randomized trial, including 114 EMS agencies, 23,711 adult patients with non-traumatic OHCAs were assigned for primary analysis either to an intervention group (continuous CCs with asynchronous ventilation, n=12,653) or a control group (30:2 interrupted CCs with synchronous ventilation, n=11,058). Continuous CCs with asynchronized ventilation comprised a series of three cycles

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of continuous CCs without ventilation pauses followed by rhythm analysis until the ROSC or completion of three cycles of CPR, whichever occurred first. Interrupted CCs with synchronous ventilation comprised a series of three cycles of standard CPR, each cycle further comprised sets of 30 CCs with ventilation pauses at compression: ventilation ratio of 30:2. In either patient group, the duration of manual CPR prior to the first rhythm analysis was 30–120 s. This treatment period was followed by two cycles of manual CPR and rhythm analysis (each approximately 2-min long) in either group. Each cycle was followed by rhythm analysis until ROSC or three cycles of CPR, whichever occurred first.

During the active-enrollment phase, 1,129 of 12,613 patients (9.0%) in the intervention group and 1,072 of 11,035 patients (9.7%) in the control group survived to hospital discharge (after adjustment for cluster and sequential monitoring, P=0.07). Of the patients with data concerning neurological status, 883 of 12,560 patients (7.0%) in the intervention group and 844 of 10,995 patients (7.7%) in the control group survived with a modified Rankin scale score of 3 or less (after adjustment for cluster, P=0.09). However, patients in the intervention group were significantly less likely than those in the control group to be hospitalized (P=0.03). Furthermore, hospital-free survival was significantly shorter in the intervention group than in the control group (P=0.004). According to these results and those of subgroup analyses, the study group concluded that continuous CCs during CPR performed by EMS providers did not result in significantly higher rates of survival or favorable neurological outcomes.

The results of this trial are not surprising when we consider that this prospective randomized study included CPR-process monitoring and quality assurance in both intervention and control groups and that intervention was conducted in patients with non-EMS-witnessed and non-traumatic OHCA after arrival at EMS. However, the results of this study clearly did not conform with those of many previous observational studies (10-13) or recommendations from the latest AHA guidelines stating that for witnessed OHCA with a shockable rhythm, it may be reasonable for EMS systems with a priority-based, multi-tiered response to delay positive-pressure ventilation using a strategy of up to 3 cycles of 200 continuous compressions with passive oxygen insufflation and airway adjuncts (15).

As described in detail in the supplementary appendix, this protocol included CPR training and a review of optimal CPR and post-resuscitation care performance, a practical "hands-on" session, a post-training test, and additional training with feedback during a run-in phase. Presumably because of such training, the mean difference in CC fraction (the proportion of each minute during which compressions were given) among the treatment groups during the trial was very small. This may indicate the importance of continuous training in maintaining the CPR quality, characterized by the short interval between stopping CCs and delivering a shock, and the minimal interruption of CCs for ventilation and advanced life support procedures in the current standard 30:2 CPR.

This study did not determine whether there was any benefit from ventilation in EMS-witnessed OHCA because the intervention group received asynchronized ventilation. However, the results of this study may provide a warning against the over-reliance upon continuous CCs without standard positive pulmonary ventilation based on previous studies without quality assurance. Furthermore, the results suggest the need for future studies to determine optimal ventilation in patients with OHCA and develop ways of measuring the ventilation quality (including airway management) during resuscitation. For example, what is the optimal level of ventilation that provides adequate oxygenation of blood and delivery of oxygen to the critical organs? Moreover, is advanced airway management that minimizes the interruption of CCs by continuous training, which is harmful in terms of survival from OHCA (4,16,17)?

Although this study included quality assurance analysis of EMS-performed CPR, it is difficult to conduct a similar quality assurance strategy in clinical studies for bystander CPR. The quality of bystander CPR is known to be affected by many factors (18). Furthermore, it is still questionable whether compression-only CPR without ventilation is as effective as conventional CPR with ventilation (19). Our recent component analyses of compression and ventilation for bystander-witnessed OHCAs showed that ventilation is a significant component of BCPR, particularly when the etiology is non-cardiac in origin and the victims are aged less than 20 years (20). As stated in the newest guidelines (15), continuous quality improvement by identifying the problem that is limiting survival, and then by setting goals, measuring progress toward the goals, creating accountability, and having a method for change, were vital in improving outcomes from OHCAs in the community.

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Footnote

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To interrupt, or not to interrupt chest compressions for ventilation: that is the question!

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Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of death in the industrialized world, with an average global incidence of 55 cases per 100,000 person-year (1). OHCA is a major public health problem. Every 5 years leading institutions like the European Resuscitation Council (ERC) and the American Heart Association (AHA) publish the resuscitation guidelines, with treatment recommendations for OHCA based on a comprehensive review of the available scientific evidence. Despite the therapeutical advances introduced by the guidelines over the years survival remains dismally low, with average survival rates to hospital discharge below 6% for all cases, and below 12% for patients presenting initial shockable rhythms (1).

Quality cardiopulmonary resuscitation (CPR) is critical for the survival of the patient suffering OHCA. During CPR chest compressions are delivered in the center of the chest, with target depths of 5–6 cm, rates of 100–120 min^{-1} and allowing complete chest recoil. Since the 2005 update, resuscitation guidelines recommend a sequence of 30 compressions followed by a 5-s interruption for 2 ventilations, the standard 30:2 CPR. During CPR chest compressions are interrupted for various reasons including rescue breaths, rhythm analysis, pulse-checks and defibrillation. These interruptions decrease coronary and cerebral blood flow and have been associated with decreased survival both in animals and humans (2-4). Rescue breaths are critical in respiratory arrest, where hypoxia leads to cardiac arrest. In nonasphyxial arrest arterial blood is saturated with oxygen for several minutes, and rescue breaths may not be essential for survival (2,3). During the circulatory phase of the arrest (4–10 min from arrest), the generation of adequate cerebral and coronary perfusion by chest compressions maybe crucial for the survival of the patient (5). This observation leads to the introduction of the concept continuous chest compressions (CCC), i.e., CPR without pauses for ventilation.

Researchers from the University of Arizona in cooperation with the Tucson Fire Department instituted the basis of cardiocerebral resuscitation (CCR). CCR is an alternative to the standard resuscitation protocol that emphasizes the adoption of CCC. They proposed a bundle of treatment changes including 200 uninterrupted preshock chest compressions, rhythm analysis with a single shock, 200 immediate postshock chest compressions before pulse check or rhythm reanalysis, early administration of epinephrine and delayed endotracheal intubation. They first introduced CCR in 2005 in selected emergency medical services (EMS) (6-8), progressing up to larger observational cohort studies and prospective studies with historical controls (9-11). In their largest study involving 2,460 patients (10) the adoption of CCR in EMS systems almost tripled overall survival to hospital discharge from 3.8% to 9.1%, an effect observed also in patients with witnessed ventricular fibrillation (from 11.9% to 28.4%). The increase in survival rates was due to a multiplicity of factors associated to the bundle of treatment changes introduced by CCR, and may have also been due to improved CPR quality. Unfortunately CPR quality data was not recorded in these studies.

One of the advantages of CCC is the increase of bystander CPR rates, because many bystanders are unwilling to give mouth-to-mouth rescue breathing (12). However, once CPR is initiated by the bystander the advantages of

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CCC over standard CPR are unclear. Several Japanese studies have investigated the effect on survival of both types of CPR. These observational studies ranged from the initial local retrospective studies of under 5,000 cases (13,14), to nationwide prospective studies of about 50,000 cases (15,16). Bystander CPR increased survival when compared to no CPR, however no significant differences in survival with good neurological outcome were found between standard and compression only CPR. In fact, for non-cardiac arrests standard CPR was superior to compression only CPR. For arrests of cardiac origin both types of bystander CPR had comparable survival rates—6.4% *vs.* 7.1%—when CPR was delivered before 15 min, but survival was significantly higher for standard CPR—2.0% *vs.* 1.3%—when CPR was initiated after 15 min.

Increasing bystander CPR rates through the use of simplified protocols such as CCC may lead to higher survival rates (12). However, the benefits of CCC over the standard 30:2 protocol for CPR delivered by EMS services are unclear, so current ERC guidelines still recommend 30:2 CPR (17,18). The bundle of therapies introduced in the studies advocating the use of CCR result in many confounders that mask the contribution to survival of individual therapies such as CCC. The contribution to survival of CCC is further obscured by the absence of CPR quality data in these observational studies with historical controls. The study by Nichol *et al.* (19) finally sheds light on whether CCC as compared with the standard 30:2 protocol improves survival when CPR is delivered by EMS providers.

The study was designed as a crossover cluster-randomized control trial (RCT) of non-trauma related cardiac arrest treated by EMS (20), and was conducted by the resuscitation outcomes consortium (ROC). The primary outcome was the rate of survival to hospital discharge, with neurologic function at discharge as secondary outcome. The trial involved 114 EMS agencies from 8 ROC sites grouped in 47 clusters during a period of 4 years. The clusters were crossed over twice a year between the two resuscitation strategies, namely CCC (intervention group) or the standard 30:2 protocol (control group), designated as interrupted chest compressions (ICC). Patients assigned to the CCC group were to receive compressions at a rate of 100 min^{-1} with positive-pressure ventilations at a rate of 10 min^{-1}. For the patients in the ICC group pauses for two ventilations were to last less than 5 s. In total 12,613 patients were assigned to the intervention group (CCC) and 11,058 to the control group (ICC), and in both cases primary outcome data was available in more than 99.7% of cases.

The study sites acquired and reported CPR-quality data measured by the monitor-defibrillators which included variables such as rate, depth or chest compression fraction (CCF). These data was reviewed by an automated algorithm and by the research coordinator to ensure adherence to the treatment protocols, and a per-protocol analysis of the data was then conducted. The per-protocol analysis based on the automated algorithm included 6,529 and 3,678 patients in the intervention and control groups, respectively.

The characteristics of the patients, EMS providers, and hospital treatments were well balanced between the two branches of the trial. There were of course significant differences in the CPR data related to pauses in chest compressions, with significantly higher CCF (0.83 *vs.* 0.77) and less pauses in compressions (3.8 *vs.* 7.0) in the intervention group. Although significant, these differences were not as large as expected because rescuers did not strictly adhere to the treatment protocol. In the per-protocol analysis differences were much larger (0.87 *vs.* 0.73 for CCF, and 2.8 *vs.* 10.3 in number of pauses), but some pretreatment and treatment characteristics were imbalanced, with significantly higher rates of shockable rhythms and prehospital intubations in the control group.

Nichol *et al.* found no significant differences in survival to hospital discharge between the CCC and ICC groups, with survival rates of 9.0% and 9.7%, respectively. Differences in survival with good neurological outcome, defined as score of three or less in the modified Rankin scale, were also not significant with values of 7.0% in the intervention and 7.7% in the control group. In the per-protocol analysis, which ensured adherence to the treatment protocol, survival was significantly higher in the control group, with rates of 9.6% and 7.6% for the ICC and CCC groups, respectively. However, when adjusted for pretreatment confounders differences in survival rates in the per-protocol analysis were no longer significant.

Two key factors explain these results. First, by conducting a large scale RCT Nichol *et al.* were able to isolate the effect on survival of pauses for two rescue breaths, particularly in the per-protocol analysis. In contrast, previous studies introduced a myriad of changes in the treatment protocol which obscured the contribution to survival of individual treatment changes. Second, CPR quality in both branches of the trial was close to optimal, with rates around 110 min^{-1}, depths close to 50 mm and CCF above 0.7. All these CPR quality variables have been previously shown to influence survival and were not controlled for in the previously cited studies. One of the limitations of the study is the small difference in CCF between the treatment branches. However, when adherence to treatment protocols was

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checked differences in CCF were larger.

The study by Nichol *et al.* shows that pauses for two rescue breaths in 30:2 CPR are not detrimental for survival, even when the presumed cause of the arrest is cardiac. This is particularly so when CPR is delivered in the ranges recommended by the resuscitation guidelines.

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Footnote

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What can a simple measure of heart rate during temperature management tell us on the physiology and prognosis of comatose cardiac arrest patients?

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Thank you for inviting us to comment on our recently published study "Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients" (1).

Targeted temperature management (TTM) remains a central part of the post cardiac arrest management and accompanying sedation and neuromuscular blocking agents have been shown to make outcome prediction challenging (2). This calls for identification of early markers of the normal physiological response to the treatment and thereby physiological markers of stability and outcome after out-of-hospital cardiac arrest (OHCA). Our understanding of the physiological response to mild hypothermia is improving, and recent reports have suggested that a simple vital sign such as heart rate during the course of TTM may provide insights into the patients' prognosis at an earlier stage than other prognostic markers.

Background

The potential beneficial effects and physiological response to mild hypothermia after cardiac arrest in the form of TTM, have gained increasingly focus following two smaller randomized controlled trials in 2002 showing favorable outcome in comatose cardiac arrest patients from an initial shockable rhythm treated with TTM at 32–34 ℃ (3,4). The International Liaison Committee on Resuscitation recommended TTM in that range (5) and the neuroprotective treatment strategy has become widely implemented since (6,7). The TTM-trial (8) was commenced in November 2010 and completed by January 2013. The study compared TTM at 33 *vs.* 36 ℃ and found similar outcomes in terms of mortality and neurological function in 939 patients from both shockable and non-shockable rhythm (9). The recent 2015 international resuscitation guidelines have, based on these results, uniformly recommended TTM in a broader range, with the option to choose a constant target temperature of 32 to 36 ℃ (10-12).

Bradycardia during targeted temperature management (TTM)

In the study "Bradycardia during targeted temperature management: an early marker of lower mortality and favorable neurologic outcome in comatose out-of-hospital cardiac arrest patients" published February 2016 in Critical Care Medicine we sought to assess, validate and further explore an area by which increased focus has evolved in recent years, namely a possible association between lower heart rates during TTM and a favourable prognosis following OHCA. A registry study (bradycardia <40 bpm) and a smaller retrospective study (13) (bradycardia <60 bpm) had indicated an association between lower heart rates at 33 ℃ with favorable outcome in univariable analysis (13,14), although multivariable adjustment failed to show an independent association. Our research group recently

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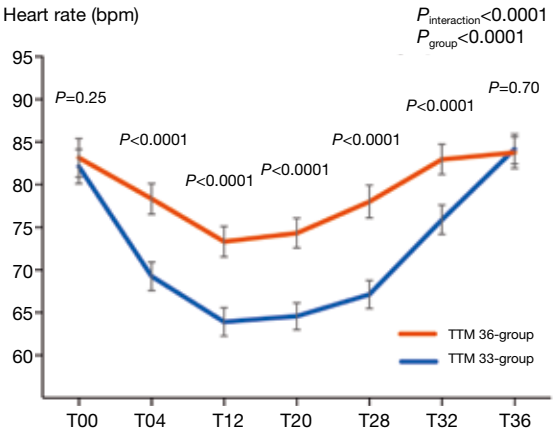

Figure 1 The mean heart rate response in comatose cardiac arrest patients treated with TTM at 33 and 36 °C. Error bars represent 95% confidence limits.

showed that sinus bradycardia <50 bpm during TTM at 33 °C was independently associated with lower mortality in a retrospective analysis of 234 comatose survivors of OHCA from an initial shockable rhythm, thereby suggesting a potential early marker of favourable outcome (15). However, these results could not readily be extrapolated to TTM targeting 36 °C, which has been implemented in many centres following the updated resuscitation guidelines (11,12).

The TTM-trial database provided an opportunity for not only validation of the proposed association in a larger cohort of OHCA-patients treated at 33 °C (15), but also a means to extend our knowledge of lower heart rates and outcome in patients resuscitated from a non-shockable rhythm and the many patients now treated with 36 °C.

In the stratified analysis of patients treated with 33 °C (*n*=447) in the TTM-trial, we found that bradycardia below 50 bpm was present in 30% of patients, whereas heart rates between 50 and 59 bpm were observed in 29% of patients. The group of patients with the lowest registered heart rates also had the lowest mortality and with a step-wise increase with higher heart rates (<50 bpm, 32%; 50–59 bpm, 43%; ≥60 bpm, 60%). Higher heart rates were more often found in patients with longer time to return of spontaneous circulation (ROSC) and higher levels of lactate on admission. When using patients with no bradycardia (≥60 bpm) as reference, patients with bradycardia <50 bpm remained independently associated with lower mortality (hazard ratio =0.50; 95% CI, 0.34–0.74; *P*<0.001), in a multivariable model adjusted for potential confounders. Similar results were found for neurological function, with lower odds (odds ratio =0.38; 95% CI, 0.21–0.68; *P*<0.01) of unfavorable outcome with bradycardia.

We found no interaction suggesting a different association of lower heart rates and outcome in patients treated with 36 °C (*n*=430), however the heart rate lowering effect was less pronounced and patients treated with 36 °C had approximately 10 bpm higher resting heart rate during TTM compared to the 33 °C group (*Figure 1*). Only 8% of the patients had bradycardia <50 bpm during TTM. In an explorative analysis of quartiles of minimum heart rates in the 36 °C group, we found that patients with heart rate below ≤57 bpm were independently associated with lower mortality (hazard ratio =0.63; 95% CI, 0.40–0.98; *P*=0.04) and lower odds of unfavourable neurological outcome (odds ratio =0.41; 95% CI, 0.21–0.83; *P*=0.01), compared to patients with heart rates ≥79 bpm (1).

Mechanisms behind the heart rate lowering effect

Hypothermia may affect the resting heart rate in various ways, including suppression of the sympathetic activity (16,17) or elevation of parasympathetic activity (16). Others have proposed that the heart rate lowering effect is mainly due to effects on the cardiac pacemaker cell, with a decrease in spontaneous depolarization (18) as discussed in our paper (1). What is known is that the heart rate lowering effect of hypothermia is present in healthy subjects immersed into cold water (16) and the markedly reduction in heart rate seen in a large proportion of comatose cardiac arrest patients during TTM may be perceived as an early marker of the physiological response to the treatment and thereby a favourable prognosis, represented by lower mortality and less neurological damage.

Comatose survivors of OHCA predominantly die from either cerebral or cardiovascular causes (19), and based on the possible causal mechanisms mentioned above of the heart rate lowering effects of mild hypothermia, it is reasonable to deduct that lower heart rates seen during TTM in post cardiac arrest care may represent a marker of both cardiac and cerebral stability with intact autonomic regulation of the heart.

In a recently published editorial regarding the importance of heart rate and its relation to the post cardiac arrest syndrome, the authors correctly point out that residual confounding may be present in the multivariable models used in our and other studies, simply due to the fact that they have not been conceptualized or due to unavailability (20). One

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of the important limitations to our studies is the lack of pre-arrest medication including beta-blockers, though patients with pre-arrest indications for such medications had a trend towards higher and not lower mortality.

Perspectives

So, to answer and discuss the question raised by the title of this commentary, "What can a simple measure of heart rate during temperature management tell us on the physiology and prognosis of comatose cardiac arrest patients?" Lower heart rates are seemingly a strong early physiological marker of favourable outcome in post cardiac arrest care, independent of cardiac arrest characteristics, comorbidity, vasopressor need and chosen temperature.

It can be speculated, based on the findings in this study, that lowering of the heart rate could be a specific therapeutic target in post cardiac arrest care for example by administering beta-blockers or ivabradine. The authors do, however, believe higher resting heart rates during TTM and a lack of bradycardic response is a physiological marker of incipient cardiac instability and/or higher degree of cerebral injury. Treating the heart rate alone would most likely be equivalent of shooting the messenger, and more benefit may be achieved by tracking down potentially reversible causes of the instability causing the higher heart rates instead. As of now, no treatment modalities other than TTM are supported for post-conditioning of the anoxic brain injury caused by the arrest, but the cardiovascular mortality seen in these patients may be reduced by early recognition of the cause of relative tachycardia. This may be facilitated by increased understanding of the physiological and pathophysiological responses to the treatment, e.g., exemplified by otherwise normal persistent heart rates above 60 bpm being associated with increased mortality during TTM at 33 ℃.

The findings further provide prognostic information to the treating physician and thereby a higher level of information to base their clinical decision-making on and this information is available earlier in the course than other established prognostic markers. This further enables more information of the patient's physiological state to be shared with the relatives, which are often eager to be informed of the patients' chances of a favourable outcome. It should however be noted that final neurological prognostication should only be made using a multimodal approach no earlier than 72 h after ROSC (2), and only when normothermia have been reached and sedation has been completely tapered.

A lack of bradycardic response in a patient during TTM, even though the heart rate may be within the normal range for a normothermic patient, could encourage the treating physician to reassess the patient for potential emerging complications or unrecognized differential diagnoses. However, whether managing these complications will lead to an improved prognosis remains to be proven.

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Footnote

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A modified Sequential Organ Failure Assessment score using the Richmond Agitation-Sedation Scale in critically ill patients

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In the January 2016 issue of *Critical Care Medicine*, Vasilevskis *et al*. (1) reported the validation study of a modified Sequential Organ Failure Assessment (SOFA) score using the Richmond Agitation-Sedation Scale (RASS) (2) instead of the Glasgow Coma Scale (GCS) for the neurological component. As explained by the authors, the SOFA score, first shown to describe multiple organ failure in patients with sepsis, is now widely used for risk stratification in a wide panel of ICU patients. Unfortunately, the GCS component is subject to implementation difficulties for some patients, such as those who are intubated, and is not highly reliable when assessing neurologic disorders such as delirium and agitation.

Vasilevskis and colleagues (1) assessed the validity of the RASS-based SOFA scoring system (*Table 1*) within the BRAIN-ICU study population, a prospective cohort study of critically ill patients admitted to medical or surgical ICUs with respiratory failure and/or shock (3). This cohort was restricted to a single center, Vanderbilt University Medical Center, for the present study. Patients who could not be assessed for delirium by study staff during the entirety of the hospital stay were excluded. Based on 513 patients analyzed, the GCS and RASS were strongly correlated (Spearman rho =0.806; 95% CI, 0.785–0.825) across all daily values. As expected, the neurologic component scores (SOFA-NeuroGCS and SOFA-NeuroRASS) were also correlated. The total $SOFA_{RASS}$ scores were strongly correlated with the original ($SOFA_{GCS}$) scores (Spearman rho =0.963; 95% CI, 0.956–0.968 for daily values) and at least moderately with other established illness severity scales.

Both the mean $SOFA_{GCS}$ and the mean $SOFA_{RASS}$ scores showed good discrimination for ICU mortality (AUC =0.799 and 0.814) and hospital mortality (AUC =0.771 and 0.782). They also showed a similar discrimination of these two outcomes when taking into account their maximum values. As noted by the authors, although the value for predicting mortality is statistically higher with the $SOFA_{RASS}$ score, this difference probably remains clinically irrelevant.

This study highlights the difficulties in carrying out the GCS in ICU patients, often intubated (4), more or less sedated, and subject to indirect brain lesion as expressed by a varied symptomatology. Good examples of this difficulty are delirium, correlated with mortality (5), and hepatic encephalopathy (6). The search for efficient scores runs into the absence of a true gold standard that can be used to compare these scales. To our knowledge, there are no biological parameters or medical devices validated to compare these scales. The bispectral index (BIS) (7-11) has been shown to be able to predict the neurologic outcome in different settings in ICU patients. It could be used as a simple, reproducible and "physiologically based" method to assess the validity of these scales. This lack of a reference combines with a common methodological problem: the use of statistical correlations for comparing scales. Since these scores evaluate the same phenomena and are for the

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Table 1 Method retained by Vasilevskis *et al.* to convert Glasgow Coma Scale (GCS) and Richmond Agitation-Sedation Scale (RASS) into the Neurologic Sequential Organ Failure Assessment (SOFA) Score

Neurologic SOFA Score	GCS Score	RASS[a]
0	15	≥0
1	13 to 14	–1
2	10 to 12	–2
3	6 to 9	–3
4	3 to 5	–4 to –5

[a], authors converted RASS from a 10-point scale to a 4-point score using three different a priori-specified methods. The method presented here, based on clinical judgment, had the best predictive validity based on its association with mortality.

most part constructed in a similar manner, it makes sense that they evolve proportionally and are correlated. Their comparison should systematically integrate a comparative evaluation of their performance on clinical outcomes.

The RASS score is a rating scale for the quality of sedation and analgesia (2), similar to the RAMSAY score (12), but in two dimensions. These scores are dependent on the patient's motor response capacity and are therefore corrupted by muscle relaxant drugs such as a curare. The BIS was developed to overcome this constraint. It has also been shown that the RASS and BIS were highly correlated (13). By analogy, they are used as a neurological severity score.

This new score, based on the RASS, is therefore a priori easier to administer in intubated (2) but non-curarized patients than the original and takes into account the agitation component.

The Vasilevskis *et al.* (1) paper provided a number of important contributions: first, there does not seem to be any loss of reliability in the short- and medium-term prediction of mortality for the patients in whom both scores are achievable. This result is reassuring in terms of its safety of use in routine practice and in future clinical studies. Second, the $SOFA_{RASS}$ does not seem to score better than the classic SOFA for predictive capacity in these patients. It is likely that this score can be administered to a greater variety of patients, which was not assessed by the study. Most importantly, it can avoid the situation in which the SOFA score is underestimated because its neurological component is ignored.

The study has several limitations concerning the choice of the test population, which may limit the results in terms of the comparative performance of the two scores. It was restricted to patients with sepsis or respiratory distress, and sedation was not prospectively modified to allow assessment of the neurological component. While this choice is understandable for a first assessment, two points should be mentioned. First, the patients included were probably not those whose assessment of the neurological component is the most important for mortality (14). For example, patients with cardiac arrest causing anoxic brain injury were excluded, and in the BRAIN-ICU study (3), patients with neurologic disease or seizure as the initial diagnosis account for approximately 1% of the initial cohort. Second, the absence of sedative cessation for the evaluation of the motor component may cause an underestimation of neurological involvement evaluated by the RASS score. We can assume that an "agitated", "very agitated" or "combative" patient as defined by the score has been administered greater sedation, which underestimates the difference with the GCS.

Notwithstanding the above limitations, Vasilevskis *et al.* have to be commended for their study. Their $SOFA_{RASS}$ score looks promising for future studies in the assessment of symptom severity in critically ill patients, especially those with potential neurological damage (1). Further investigations should aim to assess whether the score can be used in a greater number of patients than the original score, and its predictive performance in a population of patients at high risk of neurological impairment, with a prospective design limiting the effect of sedation on that assessment.

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Footnote

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Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients

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Abstract: Serum creatinine (SCr) has been widely used to estimate glomerular filtration rate (GFR). Creatinine generation could be reduced in the setting of low skeletal muscle mass. Thus, SCr has also been used as a surrogate of muscle mass. Low muscle mass is associated with reduced survival in hospitalized patients, especially in the intensive care unit (ICU) settings. Recently, studies have demonstrated high mortality in ICU patients with low admission SCr levels, reflecting that low muscle mass or malnutrition, are associated with increased mortality. However, SCr levels can also be influenced by multiple GFR- and non-GFR-related factors including age, diet, exercise, stress, pregnancy, and kidney disease. Imaging techniques, such as computed tomography (CT) and ultrasound, have recently been studied for muscle mass assessment and demonstrated promising data. This article aims to present the perspectives of the uses of SCr and other methods for prediction of muscle mass and outcomes of ICU patients.

Keywords: Creatinine; cystatin; intensive care unit (ICU); malnutrition; mortality; muscle mass

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Introduction

Creatinine is an endogenous substance generated from the nonenzymatic conversion of creatine and creatine phosphate, 95% of which is found in muscle (1). Creatinine is an uncharged, small molecular weight substance (113 Da) that is not bound to serum proteins. It is filtered freely by the glomerulus without tubular reabsorption. Creatinine is also secreted by the renal tubules only in small amounts (1).

The serum creatinine (SCr) level is ubiquitously used to estimate glomerular filtration rate (GFR) during a steady state of renal function. Although elevated SCr could be due to changes in its secretion (impact of medications: probenecid, cimetidine, trimethoprim) or production (due to increased muscle mass or meat consumption), its rise usually indicates either acute kidney injury (AKI) or chronic kidney disease. SCr-based AKI definitions have demonstrated consistent power in predicting mortality and other outcomes among the hospitalized patients (2-8). Due to the correlation between SCr levels and muscle mass, SCr in the steady state has been used as a surrogate of muscle mass measurements (9). Creatinine generation is low among individuals who have more diminutive muscle mass, either constitutionally or disease-related. Therefore, low SCr level could be considered as a proxy of protein-energy wasting in some clinical situations (10). This article discusses the perspectives of the utility of SCr and other methods as predictors of muscle mass and outcomes of intensive care unit (ICU) patients.

Mechanism of low serum creatinine (SCr) level

Low SCr levels are associated with multiple factors as shown in *Table 1* (10-15). As previously stated, creatinine generation could be reduced in the setting of low muscle mass. In the other words, malnourished individuals with smaller muscle mass have lower SCr levels. Muscle mass is

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Table 1 Factors associated with low serum creatinine levels

Low muscle mass (female gender, elderly, chronic illness)
Malnutrition
Vegetarian diet
Pregnancy
Advanced liver disease
Fluid overload
Augmented renal clearance

related to gender (females may have less muscle mass), age (advancing age may be associated with decreasing muscle mass), and ethnic background (African Americans tend to have higher muscle mass) (10). Individuals' SCr levels can also be affected by diet. Arginine and glycine are creatine precursors. Therefore, low dietary protein intake can limit creatinine generation. Also, cooked meat contains a significant amount of creatinine, which is absorbed in the intestinal tract. Thus, protein malnutrition could result in low SCr levels (11). A high GFR, as in pregnancy, could also lower SCr levels (10-12).

Patients with advanced liver diseases can have low SCr due to diminished creatinine production from decreased hepatic creatine synthesis, enhanced tubular creatinine secretion, and reduced skeletal muscle mass (12). Creatinine is distributed in total body water, and large fluid volume resuscitation, as is often required in the sickest ICU patients, could increase the volume of distribution of creatinine, resulting in lowered SCr values (13). Chronic illness, age, malnutrition, and pathologic conditions such as protein-losing disorders like enteropathies and nephrotic syndrome, also impact muscle mass and creatinine production (11).

Augmented renal clearance (ARC), an enhanced elimination of solutes by the kidneys at a rate significantly higher than normal, is a phenomenon whereby patients experience marked increase in functional creatinine clearance and GFR in acute illness; thus, leading to low SCr levels (14). With reported incidence rates ranging from 16% to 100%, ARC is commonly observed among ICU patients (15). Systemic inflammatory response syndrome (SIRS) is a common cause of ARC in critically ill patients (14).

Low serum creatinine (SCr) levels and mortality

Cartin-Ceba *et al.* (16) have previously reported the results of a large retrospective cohort study of 11,291 patients admitted to Mayo Clinic Hospital—Rochester ICUs between 2003 and 2006, evaluating the association between baseline SCr concentration at admission to ICU and in-hospital mortality. Both low and high baseline SCr levels were associated with increased in-hospital mortality. Multivariable regression analysis was used to adjust for various relevant variables including body mass index (BMI). The noted low baseline SCr was independently associated with increased mortality in a dose-response fashion. The investigators postulated that the association was due to diminished muscle mass and malnutrition.

Recently, Udy *et al.* (17) reported a large retrospective study of 1,045,718 patients across 172 ICUs by exploring data from the prospective Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation adult patient database. To mitigate the impact of volume resuscitation on SCr levels during ICU admission, the investigators stratified patients based on the peak recorded SCr concentration during the first 24 h of ICU admission, rather than the lowest SCr levels. Using a reference SCr value of 0.79–0.89 mg/dL, the investigators reported a progressively increased risk of ICU mortality at peak admission SCr levels <0.68 mg/dL and SCr levels <0.34 mg/dL [odds ratio (OR) for in-hospital mortality =2.03; 95% CI, 1.86–2.21). The study of SCr levels as a predictor of ICU or hospital outcomes is associated with limitations, as mentioned earlier. Fluid resuscitation is very prevalent in the ICU, especially within 24 h of ICU admission, so using peak SCr levels cannot completely eliminate this potential confounder. Also, low SCr levels may represent ARC; this would potentially interfere with maintaining therapeutic antimicrobial concentrations, which could be potentially associated with increased ICU mortality (14). Despite these limitations, it could be reasonably postulated that low SCr level on ICU admission reflects low muscle mass or malnutrition, which are associated with increased mortality.

Previous studies have demonstrated that high SCr levels in hemodialysis patients are associated with greater survival, whereas low SCr levels are associated with increased mortality (18,19). In the Alberta Kidney Disease Network (AKDN) study among >900,000 Canadians, Tonelli *et al.* (20) found low SCr levels with eGFR ≥105 mL/min/1.73 m^2 were associated with increased mortality. Also, low SCr levels have been correlated with cardiovascular diseases (21,22). Recently, Choi *et al.* (23) conducted a cross-sectional study of 6,986 middle-aged Korean men, which showed

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a U-shaped association between eGFR and advanced coronary artery calcification, as measured by computed tomography (CT). Compared with study individuals who had eGFRs between 75 and 89 mL/min/1.73 m^2, those with either lower or higher eGFRs were at increased risk for coronary artery calcium scores above 100. Even after adjustment for confounders, individuals with low SCr levels and eGFRs ≥105 mL/min/1.73 m^2 had an OR of 2.53 for advanced coronary artery calcification, compared with subjects with eGFRs between 75 and 89 mL/min/1.73 m^2. However, the data on proteinuria, an important marker of kidney damage, was not available in this study (23). Proteinuria, particularly albuminuria, has been shown to be associated with higher mortality and acute myocardial infarction (20). In addition, a SCr-based GFR equation is affected by non-GFR determinants of SCr including diet, muscle metabolism, and metabolic disorders. Combined analysis revealed that higher mortality in non-critically ill patients with low SCr levels likely results from malnutrition and illness, not from enhanced kidney function. Although future studies are required to assess the impact of changes in the GFR of the outcomes, in studies used cystatin C (CysC), which is independent of muscle metabolism and diet, there is a linear, not a U-shaped, association between eGFR and adverse events (24).

Muscle mass, nutritional status, and mortality

Skeletal muscle, accounting for 40% of body weight and 50% of body protein, plays a vital role in regulating immune function, glucose disposal, protein synthesis and mobility (25). Muscle provides a massive dynamic reservoir of proteins, minerals, and other intermediate metabolites that can be cannibalized to meet the need of other tissues involved in the inflammatory response. Loss of skeletal muscle and the reduced protein reservoir may predispose impaired tissue healing and poor immune function (26). As more than 75% of glucose metabolism is handled by skeletal muscle, its atrophy can impair insulin signaling, and glucose tolerance (27).

Studies have shown the reduced survival rates and the increased hospital lengths of stay of patients who have a poor nutrition status and low muscle mass (26,28,29). In patients with low muscle mass and malnutrition, cardiovascular outcomes are generally poor (30), life expectancy in cancer is reduced (31), and outcomes following liver transplantation are unfavorable (32). In elderly patients, sarcopenia, the age-associated loss of skeletal muscle mass and function, is associated with higher morbidities and mortalities (33).

Malnutrition and wasted muscles are common features in ICU patients, due to a protracted catabolic condition, correlated with high morbidity and mortality. The critical illness-related hypercatabolic state does not improve by just providing adequate nutritional support (34). Inflammatory cytokines in the setting of SIRS/sepsis have an established role in regulating muscle mass. TNF-α, IL-1, IL-6, and endotoxin infusions result in muscle wasting syndrome due to increased protein catabolism, inhibition of protein synthesis, inhibition of muscle cell differentiation, or reduced amino acid uptake (35). ICU-related respiratory muscle wasting leads to difficulties in weaning patients from mechanical ventilation (36).

Assessment of muscle mass and nutritional status in ICU

Critically ill patients require special considerations during muscle mass assessment. *Table 2* shows the typical methods used for nutritional status and muscle mass assessment in ICUs (37-48). Several studies have indicated the tools typically used to assess nutritional status are poor indicators of malnutrition in the critically ill population (37,49-51). Skeletal muscle wasting in the ICU is frequently masked by excess fat (sarcopenic obesity) (52), or by fluid retention that can amount to 10–20% of the patient's body weight (53). As discussed earlier, SCr levels are influenced by age, diet, exercise, stress, and renal disease and require cautious interpretations. Having low BMI and weight are also identified risk factors for death in ICU patients (38). Unfortunately, many ICU patients are edematous, and the measured weight and BMI may not reflect the real body muscle mass (39). Interpretation of results of other anthropometric measurements such as mid-upper arm circumference and triceps skinfold thickness also remains uncertain and of limited value to the ICU setting, as the techniques all assume a normal state of hydration (54). In addition, since ICU patients are frequently sedated, voluntary muscle strength tests cannot be performed because of impaired patient cooperation.

Albumin is also a poor marker of nutritional status, especially in the ICU setting, due to changes in intravascular volume, as well as other factors, including the impact of acute infection, inflammation, hepatic function, and protein-losing states (40). The use of tools that assess muscle mass and nutrition, such as subjective global assessment (SGA)

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Table 2 Assessment of muscle mass and nutritional status in intensive care unit (ICU)

Characteristics	Tools for muscle mass assessment in ICU	Tools for nutritional status in ICU
Body mass index (BMI)	X	X
Imaging studies including CT scan, MRI and ultrasonography	X	
Muscle biopsies	X	
Muscle strength tests		X
Neutron activation analysis (IVNAA)	X	
Nutrition Risk in Critically Ill Score (NUTRIC)		X
Nutrition-focused physical assessment (NFPA)		X
Physical assessment and anthropometric measurements (mid-upper arm circumference and triceps skinfold thickness)	X	X
Serum alanine aminotransferase (ALT)	X	
Serum albumin	X	X
Serum and urine creatinine	X	
Serum prealbumin		X
Subjective global assessment (SGA)		X

X, assessment tool.

and Nutrition Risk in Critically Ill Score (NUTRIC) (37) has been proposed. However, screening and evaluation tools often have components that are difficult to obtain in the ICU due to the severity of illness and hence cannot uniformly identify patients at risk of malnutrition (37,55). Also, performing a nutrition-focused physical assessment (NFPA) in ICU patients might not be accurate, since they frequently are intubated, sedated, and volume overloaded (55).

To date, the only two validated methods for measuring the loss of lean tissue in critically ill patients with severe edema have been *in vitro* neutron activation analysis (IVNAA) (41) and assessing differences in muscle fiber area using repeated muscle biopsies (42). The former requires radiation and is not commonly available, and the latter is time-consuming and invasive. Both methods are only used in research settings.

Imaging techniques, such as CT, magnetic resonance imaging (MRI) or ultrasound have recently been studied for muscle mass assessment (43,44). Commonly performed on ICU patients, CT scans provide a more reliable measure of muscle mass in comparison with externally measured muscle circumferences (43), in these medically ill populations. The CT images can be combined with mathematical reconstruction algorithms to estimate the mass of individual muscle groups or the total-body skeletal muscle mass. Single-slice CT images in the L3 region can predict whole-body muscle and adipose tissue volume in healthy individuals and ICU populations (44). However, CT scans are not performed on every critically ill patient, as it is costly and involves radiation exposure for prospective evaluation of body composition (44). Ultrasonography is a new and promising non-volitional measure that enables identification of changes in muscle structure and morphology (56). It is noninvasive, inexpensive, and can be performed at the bedside. Studies have also shown good inter- and intra-observer reliability (45,46). Campbell *et al.* (47) suggested that ultrasound could identify and possibly quantify muscle wasting in edematous patients with multiple organ failures. Other studies have also demonstrated that loss of muscle mass, determined by ultrasound, correlated negatively with the ICU length of stay (29,57). Also, this measurement correlates well with CT scan evaluations. While the findings are promising, further studying of assessing muscle mass by using ultrasonography to predict mortality and poor outcomes of ICU patients is needed.

Conclusions

Low muscle mass is a strong predictor of poor outcomes in ICU patients. Studies have shown high mortality in ICU patients with low admission SCr levels. Although SCr levels can be used as a surrogate of muscle mass, it is

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influenced by other GFR- and non-GFR-related factors. Further studies are needed to implement insights of underlying mechanisms of an association between low SCr and mortality in the ICU patients as well as to evaluate if aggressive nutritional support in critically ill patients with low SCr levels can improve their mortality. Studies have demonstrated promising data on the uses of CT scans and ultrasonography for muscle mass measurement in ICU patients.

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Footnote

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Utility of the Richmond Agitation-Sedation Scale in evaluation of acute neurologic dysfunction in the intensive care unit

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Multiorgan failure is common in the intensive care unit (ICU) setting with increasing mortality with greater number of dysfunctional organs. An objective assessment of the severity of individual organ dysfunction is essential for clinical care and research. Severity of illness scoring systems in the ICU have been developed over the past 30 years and are currently used widely to risk stratify patients, predict hospital mortality, perform outcome based research, assess resource utilization and measure performance improvement in patient care (1,2). The Sequential Organ Failure Assessment (SOFA) was initially devised in 1994 by an expert panel to describe severity of organ dysfunction in patients with sepsis, and has subsequently been validated as a useful marker for predicting outcomes in medical and surgical ICUs (1). Each of the six organ systems (respiratory, cardiovascular, renal, hepatic, neurologic, coagulation) are assigned values between 0 (normal function) and 4 (significant dysfunction), total scores can range from 0 to 24 (1). In the recent Third International Consensus Definition for Sepsis and Septic shock (Sepsis-3), organ dysfunction due to infection is identified as an acute change in the total SOFA score by ≥2 points. The task force has also developed quick SOFA (qSOFA) model consisting of clinical criteria (systolic blood pressure of 100 mmHg or less, respiratory rate of 22/min or greater, altered mental status) for rapid bedside identification of patients at risk of worse outcomes (3). Serial SOFA score assessments in the first 48 hours after ICU admission correlate well with mortality (4). When compared to other organ dysfunction scores, SOFA has been shown to be consistent and an accurate predictor of mortality (1). Neurologic component of the SOFA score is derived from the Glasgow Coma Scale (GCS). GCS was first developed in 1974 by Teasdale and Jennett as a tool to objectively assess consciousness in patients with head injuries and offer a standardized approach that providers could utilize to monitor neurologic exam (5). Verbal, motor and eye response in the GCS define level of consciousness. Currently, the GCS is used in a broad spectrum of medical and surgical ICU patients and is an integral part of severity of illness and prognostic scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), SOFA, Multiple Organ Dysfunction Score (MODS) and Logistic Organ Dysfunction Score (LODS) (1). However, several limitations of using the GCS in the critically ill population have been identified; including low interobserver reliability, inability to assess verbal component in tracheally intubated patients, weak prognostic value and erroneous estimation by providers due to lack of standardized assessments (6,7). The Richmond Agitation-Sedation Scale (RASS) is used for routine neurological assessments in the ICU, especially in patients without traumatic brain injury. RASS is a 10 point scale with discrete criteria, with four levels of agitation (+1 to +4), one level for calm and alert state (0), and 5 levels of sedation (−1 to −5) (8). It was initially devised to assist with administration and titration of sedation and analgesia in the ICU and has been shown to have high interobserver reliability, and consistency in estimating the patient's level of consciousness. It is easy to recall and can be administered in less than a minute with a simple three step sequence (observation, response to verbal stimulation and response to physical stimulation) (8-10). Sedation assessments based

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on the RASS are recommended by critical care consensus guidelines (10).

A prospective cohort study by Vasilevskis *et al*. (11) evaluated the validity of utilizing RASS instead of GCS to measure the neurologic dysfunction component of the SOFA score. The authors studied 513 patients admitted to either medical or surgical ICU of Vanderbilt University Hospital with a diagnosis of respiratory failure and/or shock. SOFA scores were calculated daily by using variables obtained from the electronic medical record as well as GCS and RASS measures recorded by bedside nurses during routine clinical care. The neurologic component of the SOFA score was calculated using the original GCS approach (SOFA-Neuro$_{GCS}$) and the novel RASS approach (SOFA-Neuro$_{RASS}$). The authors converted the 10-point RASS scale to a 4-point Neurologic Sequential Organ Failure Assessment Score (SOFA-Neuro$_{RASS}$). The final SOFA-Neuro$_{RASS}$ was assigned a score of 0, 1, 2, 3 or 4 for RASS scores of ≥0, −1, −2, −3 or ≤−4 respectively. RASS scores >0 (agitation) were recorded in only 0.6% of assessments and were all given a SOFA-Neuro$_{RASS}$ score of 0. Thus, final SOFA scores were obtained with the traditional GCS based approach (SOFA$_{GCS}$) and the novel RASS based approach (SOFA$_{RASS}$). These scores were calculated at study enrollment and on a daily basis until ICU discharge or death. ICU admission, maximum, mean and 48-hour change in SOFA score were also calculated.

The study showed excellent co-relation between SOFA$_{GCS}$ and SOFA$_{RASS}$ (Spearman rank correlation coefficient >0.9) for all calculated values, thus proving that the RASS score could be used instead of the GCS for calculation of the neurologic component of the SOFA score. In addition, a strong correlation was found between daily SOFA$_{RASS}$ and SOFA$_{GCS}$ was also found (spearman r=0.96, 95% confidence interval: 0.966–0.978). The SOFA$_{RASS}$ also performed well for the purposes of mortality prediction, with a moderate correlation (spearman r=0.58, 95% confidence interval: 0.52–0.64) between SOFA$_{RASS}$ and APACHE II score at study enrollment. Amongst all the calculated SOFA scores, the mean values for both SOFA$_{GCS}$ and SOFA$_{RASS}$ scores were found to be the most accurate for predicting ICU, hospital and 1 year mortality. This is not surprising given that organ dysfunction often worsens over the first few days of the ICU stay and thus the admission or day 1 SOFA score are often not predictive of outcomes.

It is interesting to note that patient sedation did not appear to affect the utility of the RASS score in assessing severity of neurologic dysfunction. The most likely explanation may be the fact that heavily sedated patients (with lower RASS scores) may also be the sickest. Thus the lower RASS scores may be an accurate reflection of their illness severity. How is the clinician to interpret the results of this study? The first point that needs to be highlighted is the fact that organ dysfunction scoring is a dynamic process. Scores obtained on admission or the first 24 hours after ICU admission may not be reflective of illness trajectory and ultimate outcomes. The 2nd point to note is the somewhat limited applicability of these scores for real time clinical decision making. This is reflected by the fact that the SOFA$_{GCS}$ and SOFA$_{RASS}$ scores in this study had an area under the curve (AUC) of 0.77 and 0.78 respectively for the prediction of hospital mortality. These numbers are not accurate enough to be of use for beside prognostication or clinical decision support tools. Another important point to note is that the study was conducted in a single institution that has been at the forefront of 'light' ICU sedation practices and the results may not be applicable to other settings and patient populations.

A more general limitation of using arousal and response based scores such as RASS and GCS alone to evaluate acute neurologic dysfunction is the inability to reliably account for the presence of delirium, which adversely impacts outcomes in the ICU population (12,13). Although the RASS score and modified RASS score have been studied for the detection of delirium in the emergency department and medical floors (14,15); the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (16) remains a more validated tool for delirium detection in the ICU. An important diagnostic feature of delirium is the presence of inattention, which can manifest as the inability to make or sustain eye contact. RASS assessment may thus correlate with the CAM-ICU, as they both capture duration of eye contact (9). Future research should be directed towards developing comprehensive neurologic monitoring tools that help better define acute neurologic dysfunction by incorporating the presence of delirium into prognostic and severity of illness scoring systems in the ICU.

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Footnote

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Serum lactate level as a useful predictor of clinical outcome after surgery: an unfulfilled potential?

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The worldwide diffusion of point-of-care testing has made it possible to assess blood lactate easy and fast, but the use of blood lactate monitoring for risk assessment in the critically ill patient remains controversial. The different policies between hospitals and departments reflect the controversy regarding the usefulness of the blood sample (1). Lately, interesting papers about blood lactate level as a predictor of clinical outcomes have been published, but if we consider the whole literature scenario we do not have enough data to consider lactate a totally reliable prognostic index, or at least not in all the clinical settings (2-8). Lactic acid is normally considered a molecule with an excellent sensitivity for the cellular damage caused by anaerobiosis due to an oxygen debit during a shock status. In this context, the lactate is an extremely sensitive parameter but not so specific, in other words, if a state of shock is always, by definition, associated with hyperlactatemia, this relation is not bijective. In current practice, lactate is frequently measured in many kinds of patients, usually with the goal of detecting tissue hypoxia. However, given the metabolism of lactate and the effect of acute illness on glucose metabolism, increased lactate levels can reflect more than only tissue hypoxia (9). The lactate is at all times the result between the cellular lactate production and its clearance by enzymatic activity. There are many causes of hyperlactatemia (10,11), that are particularly common in critically patients hospitalized in intensive care unit (ICU) ward; in those patients the lactate measurement is undoubtedly considered routine "point-of-care" analysis. It follows that the retrospective statistical analysis of this biomarker is particularly delicate and difficult if not placed in a precise clinical context. The study by Creagh-Brown *et al.* (12) has addressed this issue with a very careful design: large cohort; relevant number of participating centers from the same country, well selected inclusion criteria, precise end-point, and multivariate data analysis. The increase in mortality of patients with high lactacidemia in the 24 hours after major gastrointestinal surgery represents an expected result already reported in other studies (13). The use of the recorded blood lactate peak in the first 24 hours is the first peculiarity of the present analysis, this fact is relevant and useful for a consistent statistical analysis but it does not reflect the behavior during the 24 hours. In other words, the same blood lactate peak could be recorded at the beginning of the 24 hours and then decreases or recorded at the end of the period of observation with a diametrical different clinical significance. This technical "bug" reflects the main limitation of a retrospective study with a "point of care" parameter analysis, routinely measured in ICU as included in a simple blood gas test. The elaboration of a risk-predictor-model involving lactacidemia in patients admitted in ICU after major surgery has to consider a similar scheme reported in *Figure 1*. Furthermore, the most unexpected data is the same behavior of the mortality rate related to the lactate peak in both study groups (elective and emergency). This would consider the lactate as an absolute predictor of poor outcome even in situations in which the

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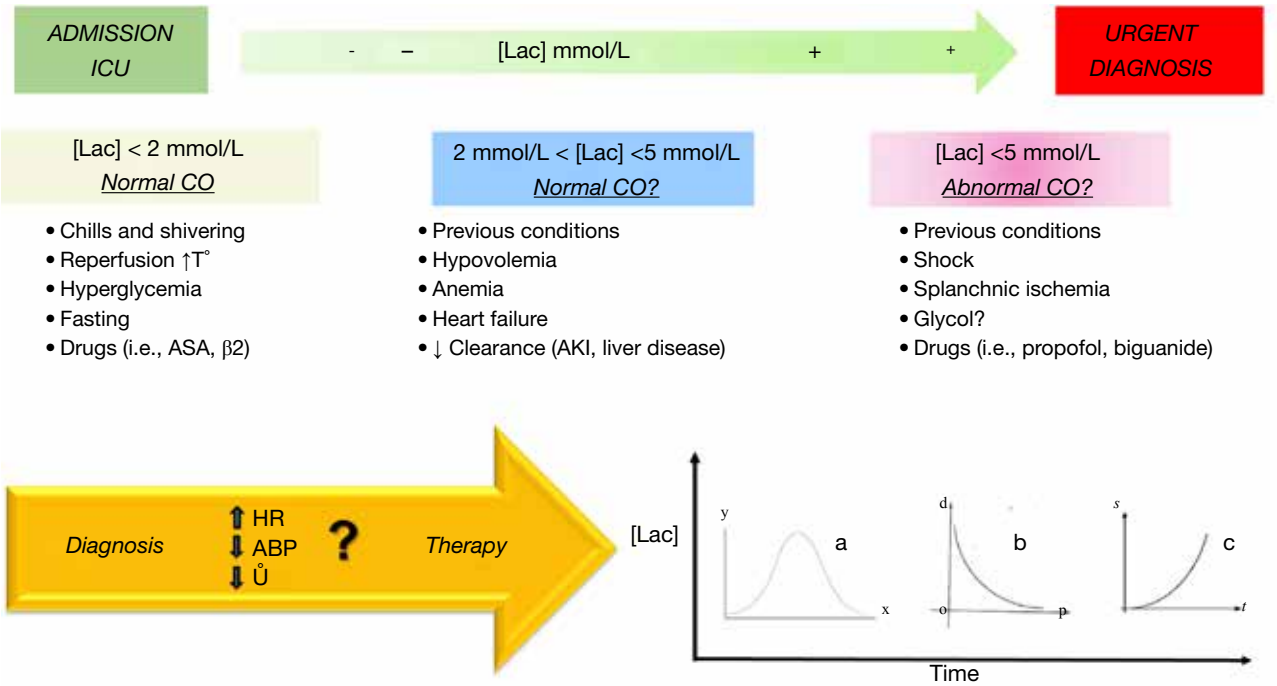

Figure 1 Possible behavior and causes of the lactic acid plasma level in the postoperative patient admitted in ICU after major surgery. The lactacidemia is divided in three groups at the admission in ICU: inferior to 2 mmol/L; between 2 and 5 mmol/L and superior to 5 mmol/L. Hyperlactacidemia requires a rapid diagnostic classification, in order to start the correct treatment. The time trend of the lactacidemia (a, b, c) is related to the physiopathological mechanism and to the efficacy of the treatment, this time trend has to be considered in the design of a risk-predictor-model using lactacidemia as a predictor of clinical outcome. ICU, intensive care unit; Lac, lactate; CO, cardiac output; ASA, acetylsalicylic acid; AKI, acute kidney injury; HR, heart rate; ABP, arterial blood pressure; Ů, urinary output.

high blood lactate level is caused by the hyper-activation of the glycolytic pathway leading to stressful situations. Moreover, Creagh-Brown and coworkers observed that, when restricting the analysis to patients with lactate peak levels within the reference range (0.1–2 mmol/L), lactate still remained an independent predictor of in-hospital mortality. This finding confirms previous observations in septic shock patients (14) and suggests mortality is proportional to the level of blood lactate without a clear safe threshold (15,16).

In substance blood lactate level remains only a partially understood biomarker, for sure it would be able to reveal much more than a cellular oxygen deficit due to a shock condition. The mitochondrial enzymatic systems are responsible of the production of the lactic acid in the cells, lactacidemia is the result of the synthesis/clearance of the lactic acid, it follows that high blood lactate levels are always expression of adverse biochemical changes and, anaerobiosis due to a shock condition represents just one possible mechanism of these adverse biochemical changes. As we said, increased blood lactate levels are common in critically ill patients. Although hyperlactacidemia is frequently used to diagnose inadequate tissue oxygenation, other processes not related to tissue oxygenation may increase lactate levels. Especially in critically ill patients, for instance increased glycolysis may be an important cause of hyperlactatemia (*Figure 1*).

In conclusion, many variables measured in critically ill patients have been used to estimate severity of disease, prognosticate morbidity and mortality, evaluate costs of treatment, indicate specific treatment, and finally monitoring the adequacy of treatment and its timing. To understand the importance of an increased lactate level, it is crucial not only to consider anaerobic production but also aerobic mechanisms and changes in lactate clearance. Despite this complex evaluation, increased lactate levels usually reflect increased morbidity and high mortality. We believe lactate monitoring is a valuable tool in critically ill patients but we need further studies to systematize the use of this parameter with an unfulfilled potential.

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Lactate: the Black Peter in high-risk gastrointestinal surgery patients

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Lactate arises from metabolisation of glucose to pyruvate. Pyruvate either is transformed to or from lactate in the cytosol or converted by pyruvate dehydrogenase in mitochondria to acetyl coenzyme A which enters the Krebs cycle to produce energy for cellular metabolism. Any switch to anaerobic metabolism will reduce activity of the highly oxygen-dependent Krebs cycle and shunt "redundant" pyruvate towards lactate (1).

Why is this seemingly trifle lactate molecule so important in the intensive care unit (ICU)? Increased blood lactate concentrations are dreaded by ICU physicians since they are almost invariably linked to the presence or persistence of inadequate tissue perfusion and oxygenation. Hyperlactatemia at a cut-off value between 2 and 4 mmol/L is associated with worse outcome in all types of shock. As such, the blood lactate level has become a powerful "biomarker" to predict morbidity and mortality as well as a tool to guide resuscitation in hemodynamically compromised critically ill patients (2). However, lactate may also be produced independently from tissue hypoxia in conditions characterized by decreased pyruvate dehydrogenase activity (e.g., thiamine deficiency), modification of the cellular redox potential (e.g., ketoacidosis, ethanol abuse), or accelerated glycolytic flux (e.g., induced by drugs such as catecholamines and biguanides) (3).

Monitoring lactate has been progressively introduced in the postoperative setting. Blood lactate concentration proved to be an indispensable and accurate marker of mortality at both individual patient and patient cohort level after cardiac surgery (4). An early lactate increase was also found to predict complications after elective pancreatic (5) and extensive liver surgery (6). However, the association between lactate concentrations and mortality with regard to type of gastrointestinal (GI) surgery (emergency *vs*. elective) remained unexplored. Hyperlactatemia following elective GI surgery was intuitively accepted as a relatively "physiological" reaction to surgical stress. Indeed, a GI surgical intervention itself will cause activation of coagulation and inflammatory pathways which can be further accentuated by procedure-related gut manipulation, temporary ischemia, and eventual bacterial translocation and shedding. In contrast, elevated lactate during emergency GI surgery was traditionally linked to a more frequent occurrence of peri-operative hemodynamic instability and resuscitation-associated ischemia-reperfusion disorders.

Li *et al*. studied dynamic postoperative changes in blood lactate levels during the first 24 h after elective major abdominal surgery. They found that time-weighted average lactate at a cut-off level as low as 1.5 mmol/L was independently predictive of both overall and major postoperative complications observed in nearly half of the patients (7). These findings have now been corroborated and expanded by the recently published study of Creagh-Brown *et al*. in *Critical Care Medicine*. These investigators showed that the highest lactate level obtained on the first day after

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ICU admission in patients who underwent major GI surgery was independently associated with increased morbidity and in-hospital mortality. This association was not related to the type of intervention (emergency *vs*. elective) and also continued down into the "normal lactate concentration" range (8). The key message of Creagh-Brown *et al*. is that any increase in postoperative lactate after high-risk GI surgery is a "bad" prognostic sign. It can be assumed that the increase in lactate after major GI surgery is related either to an overt imbalance between oxygen delivery and consumption (as in shock accompanying emergency surgery) or to a systemically occult deficit in tissue oxygen handling (as in elective surgery). Microcirculatory alterations that hamper gut oxygen extraction have been incriminated as the main culprit to explain insidious tissue oxygen debt during elective surgery. Increased blood lactate levels have indeed been shown to reflect microcirculatory dysfunction after general or thoracic surgery (9). However, changes in microcirculation during abdominal surgery were found to be rather modest and not correlated with perioperative lactate levels (10).

The findings of Creagh-Brown *et al*. do have important clinical implications. Interventions aimed at increasing gut perfusion or altering glycolytic flux during GI surgery should be promptly implemented in an attempt to lower deleterious lactate levels. The question is how this can be adequately and safely achieved. Glycolytic flux could be modulated by insulin administration but such treatment is controversial and may have significant and often unwarranted effects on glucose homeostasis (11). Lactate elimination in GI surgery patients could be enhanced by boosting oxygen delivery with a combination of intravenous fluids and inotropes. However, results of such "goal-directed" therapy after major surgery are conflicting (12,13) and probably benefit only those patients with the highest risk profile (14). Also, pursuing lactate normalization at all costs in the absence of other signs of tissue hypoperfusion may expose patients to the toxicity of over-resuscitation without any clear benefit. Nevertheless, lactate-driven adjustment of intravenous fluid administration intraoperatively and in the early postoperative period allowed early detection and correction of inadequate tissue perfusion and significantly decreased the overall complication rate after elective surgery for GI malignancy (15).

The study of Creagh-Brown *et al*. has some important limitations. First, the authors measured peak lactate levels within 24 h after ICU admission. Lactate levels result from a dynamic balance between lactate production and clearance. Therefore, serial lactate sampling is preferable to a single value since changes in lactate concentration may significantly lag behind clinical interventions, a transient increase in blood lactate does not necessarily predict poor clinical outcome, and sustained hyperlactatemia is associated with an even worse prognosis (16). Second, resuscitation policy (in emergency surgery) and routine surgical and anesthesiology procedures (in elective surgery) may have differed substantially between hospitals, hence introducing potential bias into the lactate/outcome relationship. For instance, artificial colloids can augment the risk of perioperative hemorrhage by more than 50% (17) while a sustained positive fluid balance in the early postsurgical period may significantly increase infectious complications and mortality in critically ill surgical patients (18). Also, the grade of intestinal mucosal damage and corresponding high lactate concentrations have been found to be directly correlated with the duration of surgery (19). Third, the study results were adjusted for age, severity of illness, and cardiopulmonary resuscitation status. However, in-hospital mortality may be determined by other variables that were not registered such as co-morbidity and complications either related (e.g., suture detachment or leakage necessitating revision), or unrelated to surgery (e.g., ICU-acquired infection or organ failure).

Despite these shortcomings, the study of Creagh-Brown *et al*. underscores that occurrence of increased blood lactate in the immediate postoperative period after major GI surgery is an ominous sign that requires close monitoring and adequate therapeutic anticipation. Future research must determine which intervention(s) best counteract hyperlactatemia after planned or acute GI surgery without harming the patient.

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Can the critical-care pain observation tool (CPOT) be used to assess pain in delirious ICU patients?

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Critically ill patients frequently experience both procedural pain and pain at rest. Chest tube removal, tracheal suctioning, wound care, turning and arterial line insertion have been shown to be the most painful procedures (1,2).

Untreated acute pain in adult ICU patients can lead to short- and long-term physiological and psychological complications such as postoperative myocardial infarction, insufficient sleep and posttraumatic stress disorder (3-6). Practice guidelines recommend an individualized and goal directed pain management. This includes a systematic assessment of pain with a validated pain scale appropriate to the patient's level of consciousness. Pain assessment in critically ill patients is a challenge due to mechanical ventilation, severe illness, administration of sedatives and analgesics or a decreased level of consciousness. When a patient's self-report is unachievable, validated behavioral pain scores are advised for the assessment of pain in this particular group of patients (6,7).

Two independent systematic reviews compared the psychometric proportions of pain assessment scores for intensive care patients who are unable to self-report pain (8,9). The critical-care pain observation tool (CPOT) and behavioral pain scale (BPS) received the best scores in their quality assessments and both scores are recommended in recent clinical practice guidelines for the assessment of pain in nonverbal critically ill adults (7,10,11). The CPOT was developed for the assessment of pain in critically ill patients. The scale consists of four behavioral domains: facial expression, body movements, muscle tension and compliance with the ventilation for intubated patients or vocalization for extubated patients. Patient's behavior in each domain is scored between 0 and 2. The possible total score ranges from 0 (no pain) to 8 (maximum pain). The CPOT cutoff score was >2 during nociceptive procedures (7,12).

A limitation of the CPOT is the lack of sufficient research in delirious critically ill patients. Delirium is a common complication in ICU patients and the incidence of delirium after cardiac surgery varies between 3–55% (13). The overall incidence in critically ill patients is on average 30–50% (14). Self-report of pain in this vulnerable group of patients is complicated because of the limited communication, the variable level of consciousness and a potential different presentation of pain. As a consequence, validation of a behavioral pain score like the CPOT in delirious critically ill patients is warranted (8). Kanji *et al*. addressed this problem and investigated the validity and reliability of the CPOT in adult critically ill patients with a delirium (15). They included 40 ICU patients in which delirium was positively assessed with the confusion assessment method-ICU (CAM-ICU) and excluded patients who were unable to show a reliable physical response to pain. The authors thoroughly evaluated several important psychometric proportions of the CPOT like the discriminant validation, the interrater reliability, and the internal consistency. Discriminant validation is the assessment of the ability of a scale to discriminate between different conditions or groups. Pain scales are often tested by comparing

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the score between a painful and non-painful procedure. The interrater reliability is the degree of agreement between different raters on different occasions (8,16). The authors choose a non-invasive blood pressure measurement as a non-painful procedure and repositioning, endotracheal suctioning or a dressing change as the painful procedures. The mean difference between baseline and painful procedures was 3.13±1.56 (P<0.001). The interrater reliability was based on 120 paired assessments between one of two members of the study team and an independent nurse who was not familiar with the patient. The authors tested the interrater reliability by the calculation of weighted kappa coefficients, spearman correlation coefficients and intraclass correlation coefficients (ICC) for the individual domains and the overall CPOT score. All coefficients had substantial to almost perfect agreement for the individual domains and the overall CPOT score. Kanji *et al*. concluded that their study indicates that the CPOT is a valid and reliable tool for the detection of pain in non-comatose, delirious adult ICU patients.

Although this study was meticulously designed and executed, a firm conclusion on the use of CPOT in delirious patients cannot be made yet. In this study a point of concern is the lack of data about the severity of delirium, the subtype of delirium and the relation between the Richmond Agitation-Sedation Scale (RASS) and CPOT score. The DSM-V subdivides delirium in three subtypes: (I) hyperactive form; (II) hypoactive form; and (III) mixed form. The hyperactive form is characterized by increased vigilance, restlessness, aggression and intense emotions, such as anger or anxiety. The hypoactive form is characterized by reduced alertness, sparse speech and apathy. In patients suffering from the mixed form, hyperactive and hypo - active periods alternate with each other. Peterson *et al*. defined the three subtypes according to the RASS scores (17). A hyperactive delirium was present when the RASS was persistently positive (+1 to +4). Pain and agitation may interfere in delirious patients resulting in a higher CPOT due to agitation instead of pain. In addition, the interference of sedation needs further investigation (9). Kanji *et al*. reported a median RASS of 0 with a range from –3 to +3 which shows that they included a number of patients with anxious or apprehensive movements (RASS +1), patients with frequent non-purposeful movements or patient-ventilator dyssynchrony (RASS +2) or patients pulled on tube(s) and had aggressive behavior toward staff (RASS +3). All four domains of the CPOT may potentially have been affected by high RASS scores, which might result in inappropriate high CPOT scores. These high CPOT scores may lead to additional use of analgesics were anti-delirium medication would be more appropriate. A recent study about the validity of the CPOT and BPS showed in a subgroup of seven agitated patients (RASS +1) non-significant increases in CPOT scores between rest and the painful procedure but no difference at all between the non-painful procedure and the painful procedure. The baseline CPOT score in this small subgroup was also higher than patients with RASS < +1 (18). Although this was a very small sample it is a signal that the validity of the CPOT in patients with a hyperactive delirium and/or RASS > +1 requires further investigation.

In contrast to previously performed research, Kanji *et al*. reported the interrater reliability of the four domains of the CPOT instead of the interrater reliability of the different procedures (painful *vs*. non-painful or rest). A drawback of this method is that it does not comply with daily ICU practice since the CPOT is used as the sum of four domains during different occasions like tracheal suctioning or rest. The interrater reliability of the CPOT in delirious patients during different procedures is therefore still unknown.

In this study and several previous studies, either one of the investigators or the physicians participated in the assessments. However, in daily practice a large group of nurses assess pain in the intensive care. In addition, the bedside nurse potentially interprets the patient's reactions better because of a longer contact time. Hence, more raters should be used in the assessment of interrater reliability in future studies (10). Finally, there are at least six versions of the ICC and they can give different results when applied in the same data (16,19). The authors did not report which model of ICC was used in the analysis and thus it is unclear whether they used the appropriate ICC model.

In conclusion, the study of Kanji *et al*. is an important first step in the validation of the CPOT in critically ill patients with a delirium. However, assessment of the interrater reliability of the CPOT should reflect daily practice in IC. Studies with a larger sample of delirious patients, and sufficient subsets of the three subtypes of delirium and RASS > +1, are obligatory before we can conclude that the CPOT is a valid and reliable pain assessment tool in ventilated critically ill patients suffering from a delirium.

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Footnote

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The impact of sedation protocols on outcomes in critical illness

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Critically ill patients often require pharmacologic sedation to treat pain, agitation, and delirium or to tolerate mechanical ventilation and invasive procedures (1). Over the last several decades, our understanding of medications commonly administered for sedation in the critically ill has increased and we now appreciate both the short and long-term consequences of prolonged exposure to these agents. In fact, the Society of Critical Care Medicine recently revised its sedation guidelines based on emerging evidence that certain sedation practices may influence outcomes in critical illness (2). For example, it has become quite clear that prolonged exposure to benzodiazepines and, to a lesser extent opiates, contributes to the development of delirium, while the use of dexmedetomidine might decrease the risk. However, it would be premature to suggest that we currently know enough to protocolize "optimal" sedation algorithms. Despite this recent interest in dexmedetomidine as a "delirium sparing" sedative-hypnotic, a recent meta-analysis concluded that no definitive conclusions on the use of dexmedetomidine can be drawn yet and more clinical trials seem warranted (3). In any case, delirium is associated with increased mortality, prolonged stay on the intensive care unit (ICU) and the development of post ICU cognitive impairment, and the search for new strategies to prevent or treat delirium is currently an area of intense investigation (4).

Several studies suggest that the use of dexmedetomidine or propofol, rather than a benzodiazepine, to sedate critically ill patients may reduce length of stay in ICUs or the duration of mechanical ventilation. In a large retrospective study, Klompas *et al*. found that dexmedetomidine was associated with shorter time to extubation than propofol (1). However, whether or not this difference is clinically relevant (aside from cost), or more specifically whether this difference is associated with either short-term or long-term mortality, remains unclear.

Interestingly, while dexmedetomidine reduces the duration of mechanical ventilation compared with midazolam or propofol, an increase in adverse effects has also been observed with dexmedetomidine sedation regimens (5). Bradycardia and hypotension are well-described side-effects of dexmedetomidine and in clinical practice appear to be observed relatively frequently during dexmedetomidine sedation. In addition, dexmedetomidine might not be suitable as a single agent for deep sedation. Nevertheless, numerous outcome studies focusing on sedation algorithms in critically ill patients clearly find that protocolized sedation pathways, utilizing standardized, validated patient assessment tools, can reduce ventilator days, ventilator-associated pneumonias, and delirium and hospital length of stay (5-9). It is important to note that many of these pathways include 'wake up and breathe' protocols that are not focused only on sedation agents, but also on a strict schedule of daily sedation interruption (10).

Based on this accumulated evidence that sedation protocols reduce the incidence of several adverse outcomes, it is quite surprising that information on long-term mortality is scarce. Studies that have explicitly evaluated long-term mortality have not found significant differences in mortality between different sedation and weaning protocols (1,11). A possible explanation might be the multifactorial nature of "critical illness", which can be caused by so many different factors, including hospitalization, dementia, delirium, pain, sedation, polypharmacy, organ dysfunction, metabolic and electrolyte disturbances, brain injury, trauma,

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oxidative stress, hypoxemia, ischemia, or infection (4). Moreover, while we seem to understand the influence of sedatives on the development of delirium or the duration of mechanical ventilation, essentially nothing is known about the molecular mechanisms underlying these phenomena. Confronted with this void, it seems clear that basic science research has a crucial role to play in this important aspect of intensive care medicine.

While there have been few mechanistic studies in critical illness, it is known that critically ill patients, and in particular patients diagnosed with sepsis, have a very distinct metabolic phenotype (12). In particular, mitochondrial dysfunction, endothelial disruption and derangements of NO synthesis have been all found to be associated with critical illness. Recent studies have now linked these defects with dysfunctional expression of circadian rhythm proteins (13-15). Indeed, a very common and significant feature of critical illness is a severe disruption of circadian rhythms with altered sleep-wake cycles and cognitive dysfunction (16). Moreover, medications used in the care of critically ill patients such as benzodiazepines, which have been implicated in the pathogenesis of delirium and prolonged mechanical ventilation, might also be the drugs responsible for disrupting circadian rhythms in those patients (13,14,17). Melatonin, secreted in a circadian manner by the pineal gland, is a well-established marker of a functional circadian rhythm. It is not surprising, then, that critically ill patients not only have altered sleep patterns but also abnormal melatonin levels. Recent studies of melatonin expression have therefore generated an interest in the use of exogenous melatonin and melatonin agonists to improve sleep and cognitive function in critical illness. Indeed, a promising randomized controlled trial demonstrated effectiveness in the use of a melatonin agonist (Ramelteon) versus placebo in the prevention of delirium. In the context of a possible melatonin-circadian rhythm-clinical disease axis, studies on endogenous and exogenous melatonin, pharmacological agonists, and associated genetics could provide important insight into the development and treatment of critical illness (13). Interestingly, a recent trial found that long term enteral melatonin supplementation may result in a decreased need for sedation, with improved neurological parameters and cost reduction (18). Similarly, another study on weaning from mechanical ventilation found that delirium is frequent at the initiation of ventilator weaning and is associated with a prolongation of weaning and an alteration in the circadian rhythm of melatonin excretion (19). However, it remains to be seen if melatonin agonists will be circadian disruption's silver bullet. In fact, we have to fully understand the impact of many common clinical scenarios on circadian rhythms, including severe illness, stress, noise, surgery, sepsis, drugs, nighttime exposure to artificial lighting and much more. It hardly needs to be pointed out that a single therapy might not be sufficient to restore disrupted circadian rhythms in critically ill patients. More likely, implementation of a circadian "care bundle", (for example, a combination of melatonin agonists, targeted daylight exposure in the ICU during daytime hours, and reduced exposure to noise and artificial light during the night) together with optimized sedation and weaning protocols, will offer the best hope of restoring disrupted circadian rhythms, and eventually might improve mortality in critical illness (14).

While we will have to wait for clinical trials testing such a multimodal therapeutic approach, there is little doubt that circadian rhythms have important impacts on human health and disease. Recent evidence suggests that disrupted circadian rhythms increase the risk of many common diseases, including myocardial infarction, stroke and sepsis (14). Moreover, the two-hundred most commonly prescribed medications in the United States have at least some circadian aspect to their pharmacology (20). In fact, chronotherapy, the administration of medication at very distinct time points during the day, is a well-established approach in a few areas, but not established in everyday clinical practice, including pharmacotherapy in critical illness. Future studies in critically ill patients should begin to record the time points when certain interventions are performed for analysis of circadian effects. In addition, continuous drug infusions or feeding strategies will need to be critically evaluated in future ICU studies.

In summary, sedation and weaning guidelines seem to improve outcome parameters in critically ill patients, but overall morality reduction has yet to be convincingly demonstrated. Based on the complex, multifactorial origins of critical illness, a multimodal therapeutic strategy seems more likely to be effective. Future research will need to consider the influence of circadian rhythms on both critical illness and ICU sedation if we ever hope to find "optimal" sedation strategies.

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Footnote

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The best sedation drug—a quest for the holy grail?

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Over the last 15 years, knowledge on sedation has increased substantially and as a result, the paradigm of sedation practices has moved entirely from a deep sedated, unconscious patient to an awake, collaborative and moving ventilated patient. Over-sedation is increasingly recognized as a cause morbidity resulting in an extended length of stay and longer duration of mechanical ventilation. Early deep sedation has also been associated with higher in-hospital mortality in an observational study performed in 45 Brazilian ICUs (1). Reflecting the current evidence, the most recent guidelines of the Society of Critical Care Medicine recommend titration of sedatives to achieve light sedation unless clinically contraindicated (2).

Besides the depth of sedation, agents commonly used have also been a source of criticism in the last decade. In contrast with previous guidelines where the use of lorazepam was the primary sedation option (3), current guidelines recommend benzodiazepine-sparing drugs to reduce acute brain dysfunction and time on the ventilator (2). This recommendation was based on the studies that concluded that benzodiazepine use was associated with a higher risk of developing delirium/coma (4,5). Recent meta-analysis suggests that benzodiazepine-sparing sedation regimens may reduce ICU length of stay and duration of mechanical ventilation (6). However, studies until now were unable to answer whether there are significant differences between propofol and dexmedetomidine in comparison to benzodiazepines or as compared to one another (7,8). One large randomized trial of a mixed population of critically ill patients (PRODEX) showed no major benefit of dexmedetomidine use as compared to propofol regarding the duration of mechanical ventilation, the length of stay in the ICU and mortality (8).

To try to fill this gap of knowledge, Klompas *et al*. (9) evaluated 9,603 patients for over a 7-year period, comparing hazard ratios for ventilator-associated events (VAEs), extubation rates, hospital discharge, and hospital death amongst benzodiazepines, propofol, and dexmedetomidine. This is a well-designed, retrospective study, in which the authors adjust for severity and type of illness, comorbidities, time of initiation of mechanical ventilation, among other factors that could have influenced sedative choice. The authors concluded that non-benzodiazepine sedation was associated with less time to extubation compared to benzodiazepines, while, in direct comparison, dexmedetomidine was associated with less time to extubation compared to propofol and may, therefore, be a preferred agent in selected patients. No clear mortality benefit has been reported with the use of either dexmedetomidine or propofol in this cohort.

The greatest strength of this article is the large number of patients enrolled. It is also a real-world study of non-selected patients, which evaluates actual sedation practices. However, some issues should be mentioned to put the conclusions in context.

Firstly, the authors did not include data about processes of care like daily sedative interruption and goals of sedation, as well as the depth of sedation attained. As mentioned before, early deep sedation is associated with higher mortality, and it is not unreasonable to think that midazolam and propofol

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use may be a marker of profound sedation, instead of a cause of higher mortality *per se* (1). Also, sedation practices have changed substantially during the study period, favoring a benzodiazepine-sparing and analgesia-centered approach. This changing practice during the long period of the study may have led to bias in the analysis.

Secondly, reflecting the 2002 SCCM guidelines recommendations, the majority of patients have used benzodiazepines, making it difficult to compare with current prospective studies. It is not clear if this difference between propofol and dexmedetomidine would still happen in a benzodiazepine-sparing environment. On the other hand, dexmedetomidine was used mainly in surgical patients, and propofol, in medical patients. Although the authors have made comparisons between cardiac surgery and non-cardiac surgery patients, even when cardiac surgery was excluded from the analysis, dexmedetomidine was mainly used in surgical patients, who are expected to have a shorter time to extubation and length of stay. Once more, dexmedetomidine use may be a marker of light sedation in a subset of patients who are expected to be extubated shortly after arrival in the ICU.

No sedative-analgesic agent is sufficiently superior to other agents to warrant its use in all clinical situations. As a result, selection of an agent must be individualized according to patient characteristics and the clinical situation. The etiology of the distress, the expected duration of therapy, potential interactions with other drugs, the desired depth of sedation, and pharmacokinetic modifying factors are important considerations whenever selecting an agent. The article of Klompas *et al*. (9) brings new pieces of evidence to improve the selection of the best sedative agent to achieve light sedation in critically ill patients. More prospective large controlled studies are necessary to improve the understanding of the individual risk and benefits profiles of different sedatives.

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Sedative choice and ventilator-associated patient outcomes: don't sleep on delirium

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Sedation is an integral component of care for critically ill and intubated patients. The adult intensive care unit (ICU) literature suggests that the choice of sedative agent may be central to patient outcomes during and after mechanical ventilation (1). Current guidelines recommend avoidance of benzodiazepines in preference of propofol or dexmedetomidine, and highlight a preference for maintaining light levels of sedation in critically ill adult patients. These guidelines stem largely from research comparing benzodiazepine to non-benzodiazepine sedatives (2), and more specifically, dexmedetomidine to midazolam, with or without propofol (3,4). Patients who received dexmedetomidine spent less time on the ventilator and experienced less delirium. However, comparisons between dexmedetomidine and propofol are limited.

In the recent article in *Chest* entitled "Associations between different sedatives and ventilator-associated events, length-of-stay, and mortality in mechanically ventilated patients", Klompas and colleagues examine three commonly used sedatives in a "large, real world cohort" (5). The authors are to be applauded for conducting a large-scale pragmatic, retrospective cohort study to evaluate the association between use of benzodiazepines, propofol, and/or dexmedetomidine on the risk of ventilator associated events (VAEs), extubation, hospital discharge, and hospital mortality. VAEs were defined using the VAE surveillance definition algorithm (6), and classified as ventilator-associated conditions, infection related ventilator-associated complications, or the combined outcome of possible or probable pneumonia. To estimate the impact of daily sedative exposures (benzodiazepines, propofol, and dexmedetomidine) on these outcomes, the authors created proportional sub-distribution hazards models with competing risks (5). This allowed for the analysis of benzodiazepines and non-benzodiazepines (propofol and dexmedetomidine), as well as analysis between propofol and dexmedetomidine.

The investigators included in their study population all adults experiencing invasive mechanical ventilation lasting ≥3 calendar days at Brigham and Women's Hospital in Boston between 2006 and 2013. Broad inclusion criteria resulted in a large and heterogeneous study population, which the authors assert increased the study's generalizability compared to traditional randomized controlled trials examining sedative use. The large cohort studied included 9,603 consecutive episodes of mechanical ventilation and 86,714 ventilator days, with a median duration of mechanical ventilation of 6.0 days. Benzodiazepines were administered to 66% of all subjects for at least 1 day, with 62% and 12% receiving at least 1 day of propofol and dexmedetomidine, respectively. The majority of benzodiazepine use was in the form of

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continuous infusions (74%). Not surprisingly, sedatives were often used concurrently: all three agents were prescribed on 10% of ventilator days and two different agents were given on 46% of ventilator days. Of note, 57% of dexmedetomidine exposures were in cardiac surgery patients.

No association was found with time to hospital discharge or mortality when comparing all three sedatives, and benzodiazepines were associated with higher VAEs compared to regimens without exposures to benzodiazepines. In direct agent comparisons the authors found no difference, however these findings are consistent with current guidelines (1). Additionally, there is evidence to suggest that dexmedetomidine is associated with less time to extubation compared to propofol, further supporting the findings of Jakob *et al*. that patients randomized to dexmedetomidine were extubated sooner than patients randomized to propofol (4).

The limitations of the study and conclusions stem from an oversimplification of the conceptual framework and causal pathway leading to VAEs in critically ill patients. First, as the authors note, data on depth of sedation was not collected. To achieve optimal sedation management, continuous measurement of a patient's level of sedation at regular intervals is imperative; using these measures to avoid both oversedation and undersedation have the potential to reduce morbidity and mortality (7). The Pain Agitation and Delirium guidelines strongly recommend the use of a sedation scoring system to routinely assess depth of sedation and agitation in ICU patients, and the results of these sedation/agitation assessments should provide the basis for the use of sedatives in critically ill patients (1). One must temper any correlation between type of sedative and VAEs without documentation of the patients level of sedation or the patient-specific goals established by the providers. A second major limitation is that the authors fail to discuss delirium as a likely confounder on the causal pathway from benzodiazepine use to VAEs. It is possible that much of the association between benzodiazepines and VAEs is a reflection of increased delirium incidence. A recent study by Mehta and colleagues found that over 50% of mechanically ventilated adults screen positive for delirium, and that those who screen positive have a longer duration of ventilation (13 *vs*. 7 days), ICU stay (12 *vs*. 8 days), and hospital stay (24 *vs*. 15 days) (8). Benzodiazepines are a well-established pharmacologic risk factor for delirium in critically ill adults (9). Given delirium is related to both the exposure and the outcome, with increased delirium often leading to increase sedative use, it cannot be emphasized enough that delirium must be considered in any analysis of sedatives and patient outcomes.

Understanding the delicate balance between optimal sedation, sleep quality, and delirium prevention is central to improving outcomes in mechanically ventilated patients (10-12). Sleep, in all of its measurable aspects, is severely deranged in critically ill patients during mechanical ventilation, and sleep disturbance is a risk factor for delirium. Multiple patient and environmental factors in the ICU, including sedative choice, contribute to abolishing circadian rhythms and sleep-wake homeostasis (12-14). Benzodiazepines decrease restorative non-rapid eye movement sleep as well as rapid-eye movement sleep. Moreover, sleep fragmentation is known to alter patient-ventilator interaction, another possible confounder in the association between sedation choice and VAEs (13). A provider's choice of sedative can have deleterious effects on sleep, leading to a vicious cycle of increased sedation needs and ultimately delirium (10,15,16).

Recognizing these complex interactions and the importance of sleep highlights the authors' findings regarding dexmedetomidine. Unlike benzodiazepines, dexmedetomidine is known to induce a natural, sleep-like state (16). The study's results are encouraging and again support prior studies comparing dexmedetomidine and traditional sedatives. The MENDS randomized control trial by Pandharipande and colleagues found that in mechanically ventilated ICU patients (even with individualized targeted sedation management), the use of a dexmedetomidine infusion resulted in more days alive without delirium or coma and more time at the targeted level of sedation than with a benzodiazepine infusion (9). Given the growing body of evidence regarding harm associated with benzodiazepines, it is concerning to see how prevalent benzodiazepine use is in ICUs internationally. Kudchadkar *et al*. found that over 70% of intensivists' initial sedation regimen for intubated children was a combination of opioid and benzodiazepine, with midazolam being the first-line benzodiazepine 86% of the time. Interestingly, less than 1% used dexmedetomidine alone when initiating a sedation regimen (10). The adverse effects of benzodiazepine may reach further in children undergoing active neurocognitive development.

The goal of sedation management in an intensive care unit is to provide a patient with anxiolysis and comfort; however, this should not come at the expense of patient safety, restorative sleep, and delirium prevention. The authors' raised an important question regarding sedation choice and ventilator-associated outcomes, confirming

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the notion that benzodiazepine prescribing for sedation in critically ill patients should likely be the exception and not the norm. As we continue to investigate the optimal approaches to sedation and analgesia in critically ill, mechanically ventilated patients, it is crucial that pharmacology isn't considered as a silo. Downstream effects of the most commonly used sedatives, including sleep disturbances and delirium, must be prioritized in the setting of patient-specific and goal-directed sedation. This is the only path to take as we strive toward the cutting-edge of improving short and long-term outcomes for survivors of critical illness.

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The delicate balance between pro-(risk of thrombosis) and anti-(risk of bleeding) coagulation during extracorporeal membrane oxygenation

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During veno-venous extracorporeal membrane oxygenation (VV-ECMO), a pump drains blood from a large vein, moves it towards a membrane oxygenator, where gas exchange occurs, and then pushes it back into a large vein (1). Blood is thus continuously exposed to non-biological surfaces, including cannulas and membrane oxygenator, and high shear stress, mainly generated by the pump. Platelets and coagulation are activated so that systemic anticoagulation is needed to prevent thrombosis, inside and outside the body.

Despite continuous infusion of unfractionated heparin, visible clots are detected in 20% of adults treated with VV-ECMO. Thrombosis is usually not a fatal complication, not even when it requires urgent replacement of the membrane oxygenator (overall survival is 55%). Conversely, gastrointestinal and intracranial hemorrhages occur in 10% of the cases and are commonly lethal (overall survival declines to 34% and 20%, respectively) (2).

Herein we will briefly discuss hemostatic changes during VV-ECMO. First, we will describe a paper just published in *Critical Care Medicine* (3). Second, we will present our findings on this same topic. Third, we will highlight some limitations of the way we currently administer unfractionated heparin during VV-ECMO. Finally, we will present our and others ongoing research.

Hemostatic changes during VV-ECMO

Activation of platelets and coagulation during VV-ECMO depends, at least in part, on blood exposure to non-biological surfaces and high shear stress. Accordingly, it can be attenuated by covering non-endothelial surfaces with anticoagulants, by avoiding direct contact between blood and gas inside the membrane oxygenator (nowadays, gas flows inside and blood circulates outside hollow fibers) and by reducing exogenous areas and priming volumes (membrane oxygenators and circuits are becoming smaller and shorter) (4,5).

In a recent issue of *Critical Care Medicine*, Malfertheiner and colleagues examined the impact of three VV-ECMO systems on hemostasis. Fifty-four adults with severe acute respiratory distress syndrome (ARDS), mainly due to pneumonia, were assigned to the Cardiohelp (Maquet Cardiopulmonary AG, Rastatt, Germany), the Dideco ECC.O5 (Sorin Group) or the Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik AG, Rastatt, Germany). These three systems differ in non-endothelial surface covering (heparin or phosphorylcholine), type of pump (centrifugal or axial), surface area of membrane oxygenator (1.2–1.9 m^2), surface area of heat exchanger (0.14–0.45 m^2) and priming volumes (273–390 mL). Nonetheless, they produced analogue variations in hemostasis. During the first 5 days of ECMO, with extracorporeal blood flows typically <3.5 L/min, prothrombin fragment 1.2 and thrombin-antithrombin complex (markers of thrombin generation, i.e., activation of coagulation) and D-dimers (fibrinolysis) equally increased while factor XIII, fibrinogen and platelet count were similarly "consumed". These changes occurred despite continuous infusion of unfractionated heparin

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Initial bolus of UFH
70 IU/kg if basal aPTT ratio <1.5
50 IU/kg if basal aPTT ratio ≥1.5

Maintenance infusion of UFH
18 IU/kg/h, then adjusted to maintain aPTT ratio between 1.5 and 2.0

aPTT ratio	≤1.20	1.21–1.30	1.31-1.49	1.50-2.00	2.01-2.25	2.26-2.49	≥2.50
Bolus (IU/kg)	20	10	0	0	0	0	0
Stop infusion (min)	0	0	0	0	0	30	60
Dose adjustment	+20%	+15%	+10%	0	–10%	–20%	–30%
Check aPTT	2 h	4 h	6 h	8 h	6 h	4 h	2 h

Figure 1 Our current protocol for infusing unfractionated heparin during VV-ECMO. We administer unfractionated heparin (UFH) as a bolus at the time of insertion of vascular cannulas and as a continuous infusion thereafter, with an aPTT ratio target of 1.5–2.0. We normally check aPTT every 8 hours. If aPTT is not in target, we react according to a standardized protocol. For example, if aPTT ratio is lower than 1.2, we administer a bolus (20 IU/kg), we increase continuous infusion rate by 20% and we check aPTT after 2 hours. If aPTT ratio is higher than 2.5, we suspend continuous infusion of UFH for 60 minutes. We then restart it at a 30% lower rate and check aPTT after 2 hours. Heparin dosage is computed according to actual body weight. Please refer to main manuscript for further details. VV-ECMO, veno-venous extracorporeal membrane oxygenation.

with an activated partial thromboplastin time (aPTT) target of 50–60 sec. Doses of heparin and incidence of thrombotic and hemorrhagic complications were not reported but none of the membrane oxygenators had to be replaced during those first 5 days. Coagulation tests and platelet count tended to return normal after termination of ECMO (3).

These results are only partly in line with what we have observed in 12 other adults similarly treated with VV-ECMO. Unfractionated heparin was infused with an aPTT ratio (patient-to-normal clotting time) target of 1.5–2.0. No significant change occurred in several hemostatic assays, including prothrombin fragment 1.2, D-dimers, factor XIII and fibrinogen, over the first 7 days of ECMO, except for a constant decline in platelet count. Two additional global coagulation tests [thromboelastography (TEG) and thrombin generation] were not consistent with endogenous hypercoagulation (6).

Different findings possibly reflect different study populations. Malfertheiner and colleagues (3) enrolled subjects with mainly infective ARDS that largely alters coagulation and inflammation (7). By contrast, we enrolled many subjects with acute exacerbation of chronic obstructive pulmonary disease that is reasonably associated with less severe inflammation. One may then conclude that hemostatic changes during "modern" VV-ECMO depend primarily on factors other than configuration of the system, possibly including underlying disease.

Our current approach to anticoagulation during VV-ECMO

At our institution, unfractionated heparin is infused according to a standardized protocol (*Figure 1*). We administer a bolus (50–70 IU/kg of actual body weight, IV) at the time of insertion of vascular cannulas and then a continuous infusion (starting with 18 IU/kg, IV) with an aPTT ratio target of 1.5–2.0. Specific blood products are transfused if antithrombin activity is <70%, hemoglobin is <10 g/dL, fibrinogen is <150 mg/dL, platelet count is <45,000 cell/mm^3 (<80,000 cell/mm^3 in case of recent surgery) or prothrombin time ratio is >1.5.

We rely on aPTT rather than activated clotting time (ACT) because it possibly better reflects heparin dosage (8) and anti-factor Xa activity (the gold standard for monitoring the anticoagulant effect of heparin) (6) during VV-ECMO. One single-center retrospective study reported fewer, potentially lethal, bleeding complications in pediatric patients receiving ECMO when heparin infusion was guided by aPTT compared to ACT (8).

Even so, aPTT is not the ideal test for monitoring systemic anticoagulation during ECMO. It is time consuming, it is not well standardized and it is not routinely available at the bedside. The target we use is derived from guidelines for preventing thrombosis in other settings and, even there it is supported by weak evidence (9). Using a similar target in subjects with hardly predictable

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concomitant changes in hemostasis could result in unacceptably frequent bleeding. The correlation between aPTT and heparin dosage or anti-factor Xa activity, although significant, is weak (6,8). aPTT does not provide any insight on other critical variables such as factor XIII activity and platelet count and function.

To overcome some of these limitations, one could rely on additional tests, including anti-factor Xa activity (10) or, maybe, on point-of-care assays that better assess whole blood hemostasis, such as TEG (see below).

We consider replacing membrane oxygenators whenever at least two of the following criteria are met: (I) sharp increase in D-dimers; (II) otherwise unexplained large decline in platelets; (III) membrane oxygenator dysfunction; (IV) detection of large clots (10). Again, this practice is not evidence-based. Clinical suspicion alone may lead to (hazardous) replacement of membrane oxygenators that do not contain any large clot, as judged by multi-detector computed tomography (11).

Overall, it is our experience that using a protocol, as the one described above, ensures uniform decision and facilitates achievement and maintenance of anticoagulation target over time. However, one has to bear in mind that commonly available tests are not perfect. We strongly advise discussion among staff members, possibly including an expert in coagulation, whenever management of anticoagulation calls for critical decisions.

Ongoing and future research

TEG is a point-of-care test that graphically displays the viscoelastic properties of whole blood as it clots *ex-vivo*. It can be used to guide transfusion of blood products in bleeding patients, especially after trauma or during cardiac surgery (12). It can also be used to examine changes in coagulation, including fibrinolysis, during sepsis (13).

The first component of the graphical output generated by TEG is known as "clotting reaction (R) time". It represents the delay between activation of coagulation and initiation of clotting. R-time mainly depends on the balance between pro- and anti-coagulant factors and it is typically prolonged by heparin. By comparing values obtained with or without heparinase one can assess the anticoagulant effect of heparin (12).

We have recently studied the relationship between aPTT and R-time in 316 blood samples taken from 32 patients treated with VV-ECMO (14). When aPTT ratio was in target (1.5–2.0), R-time was unexpectedly high (>24 minutes, without heparinase) 80% of the times. This finding might indicate that current aPTT ratio target frequently results in excessive anticoagulation and risk of bleeding. Based on this premise, we are evaluating safety and feasibility of infusing unfractionated heparin with a R-time target (without heparinase) of 16–24 minutes during VV-ECMO (NCT02271126).

Finally, two other exciting areas of ongoing research deserve a comment. One relates to changes in platelet function during VV-ECMO. In fact, bleeding is exceptionally more common in patients treated with ECMO than in those receiving systemic anticoagulation for other reasons (15). Factors other than unfractionated heparin infusion could explain this finding. Saini and coworkers have recently noted that more than 75% of blood samples obtained from 24 children treated with ECMO had signs of severe platelet dysfunction predictive of bleeding and death (16). The other one concerns alternative ways to provide systemic anticoagulation during ECMO. Fibrin formation is normally initiated by factor XII, in response to blood contact with non-endothelial surfaces (intrinsic pathway of coagulation), or by tissue factor, in response to tissue disruption (extrinsic pathway). In rabbits undergoing 6 hours of ECMO, antibodies directed against activated factor XII prevented thrombosis of membrane oxygenators as efficiently as heparin, but without increasing bleeding from wounds (17,18).

In conclusion, systemic anticoagulation is needed during VV-ECMO and it strongly impacts on outcome. Further research is needed to optimize its use, with the aim of minimizing risk of thrombosis without increasing that of (potentially fatal) bleeding.

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Footnote

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Hemostatic changes during extracorporeal membrane oxygenation: a commentary

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Veno-venous extracorporeal membrane oxygenation (ECMO) is a technique utilized to support patients suffering from respiratory failure. Historically, ECMO has been used as a last resort life-saving procedure by a restricted group of highly specialized centers of care. Recently, interest in ECMO has risen. Technology advancements have made ECMO safer (1). The CESAR trial showed that Acute Respiratory Distress Syndrome (ARDS) patients might have better outcomes if treated with ECMO rather than conventional strategies (2). The H1N1 experience demonstrated the feasibility of implementation of ECMO even in centers with limited experience (3).

Notwithstanding these progresses, use of ECMO is guided by center-specific experiences rather than by evidence-based guidelines. This is particularly true for coagulation management. Anticoagulation policies vary widely among centers (4) and each ECMO center has elaborated its anticoagulation protocol. Most of these local anticoagulation protocols are founded on the Extracorporeal Life Support Organization (ELSO) clinical indications (5), which are a guide to safe clinical practice, but not a consensus recommendation or an evidence-based blueprint.

These difficulties stem from the lacking of knowledge of the biology of blood compatibility (6). Seminal works have shown activation of coagulation factors and complement factors, platelets consumption and impairment (7-10) leading to bleeding (11) and thromboembolic (12) complications following ECMO connection. Since then, not many studies have focused on coagulation during ECMO. Indeed, few properly performed studies evaluated the clinical impact of technological advances, such as of heparin-coated circuitry (13,14), centrifugal pumps (15) and polymethylpentane oxygenators (16). To the contrary, only recently the interest in studying the effects of veno-venous ECMO upon coagulation has re-grown (17) and provided interesting hints. In particular, Heilmann *et al*. (18) have shown that during ECMO extracorporeal blood undergoes high shear stress, leading to the uncoiling of von Willebrand factor (vWF). This in turns reduces the capabilities of vWF in binding collagen and platelets, resulting in a state of thrombosis, fibrinolysis and impaired platelet function that propagate from the extracorporeal circuit to the patient.

Malfertheiner *et al*. (19) expanded our knowledge on coagulation during ECMO. The Authors randomized a cohort of 54 consecutive adult patients with acute respiratory failure to be treated with three different veno-venous ECMO circuits (i.e., CardioHelp, Maquet Cardiopulmonary, Rastatt, Germany; Dideco ECC.O5, Sorin Group, Mirandola, Italy; Hilite 7000 LT, Medos Medizintechnik, AG, Stolberg, Germany) and extensively assessed the effect of long-term extracorporeal support upon coagulation. Notably, all these systems have polymethylpentene hollow-fiber oxygenator and two (i.e., Maquet and Medos) are heparin-coated while the latter (i.e., Sorin) is phosphorylcholine-coated. Patients were managed by continuous infusion of unfractionated heparin, targeting an activated partial thromboplastin time (APTT) of 50–60 seconds. Factor XIII, thrombin-antithrombin (TAT)

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complex, prothrombin fragment 1.2 (F1.2), antithrombin were assessed, alongside standard measurements such as platelet count, D-dimers and fibrinogen. Even if differed as regards to priming volume, membrane surface, and coatings, the ECMO systems had similar effects on coagulation status of the patients. Indeed, regardless of the employed circuitry, connection to the extracorporeal circuit was associated with a progressive consumption of platelets and with the activation of coagulation pathways as demonstrated by the drop in fibrinogen and rise in D-dimers, F1.2, TAT complexes. Interesting, such pathologic condition was reverted by ECMO termination.

As acknowledged by the authors, limitations apply to the work. First, platelet and vWF function were not assessed. Second, the application of different extracorporeal setups (i.e., higher blood flows or smaller cannulas) may expose blood at various shear stresses and thus affect blood coagulation differently. Finally, with increasing duration of ECMO treatment activation of coagulation in the circuit require to exchange the oxygenator or the entire circuit. When circuit exchange became necessary, the activation of coagulation is maximal and likely associated with the higher effects on coagulation factors. Since only the first 5 days of ECMO treatment were studied, the effects of duration of circuit and circuit thrombosis on hemostatic function remain to be investigated.

These limitations pave the way for future research. Following the cell-based model of coagulation, future research efforts should focus on platelets and their primary role in the response of blood to artificial surfaces. Innovative monitoring techniques, such as thromboelastography and aggregometry, allow for the analysis of coagulation as a whole and the evaluation of platelet activation and function, respectively. Despite being validated, these tests are reported inconsistently. We believe that the application of these techniques in the ECMO scenario may allow for a more comprehensive study of the coagulation status and the adjustment of anticoagulant therapy to the varying clinical needs of patients with respiratory failure. The consequences of the application of different extracorporeal blood flows and thus the effects of varying shear stress on coagulation-factors functionality and the uncoiling of vWF needs further analysis. Moreover, more extensive studies of novel drugs capable of the modulation of platelet function (i.e., nitric oxide, prostacyclins), direct inhibition of thrombin, antibody-mediated inhibition of factor XIIa (20) are needed. Similarly, assessment of the effects on coagulation of new polymers and technological solution (i.e., membranes, circuit materials) are warranted.

In conclusion, despite shedding new light on coagulation status during ECMO, the findings of the present work are a small step forward in the knowledge of such neglected huge topic. Influence of long-term ECMO therapy on hemostasis deserves further in-depth experimental as well as clinical evaluations.

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Challenging orthodoxy in critical care trial design: physiological responsiveness

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Research involving critically ill adults poses unique challenges in addition to the usual difficulties involved in conducting quality, replicable scientific research. The critical care research community has responded admirably to these challenges by rigorously conducting numerous large and often multicenter randomized controlled trials (RCTs) of putative therapies for critical illnesses. Yet in spite of two decades of work, few incontrovertibly efficacious therapies have resulted from this herculean effort (1). The reasons for this are unsettled, but several categories of problems have emerged. The first problem is that of "positive" trials that cannot be replicated (2-15). Since the clinical trial is in essence a diagnostic test of a hypothesis (16), these non-replicable studies represent "false positives." False positive trials are due to type I errors which are increased by selection of a conventional and lax statistical significance threshold (e.g., α=0.05) (17,18), bias in the study at any stage of design, conduct, analysis and reporting (19), and fraud (20). Recently, the center for open science collaboration demonstrated that the majority of 100 "positive" psychological research studies could not be replicated, suggesting a false positive rate of 63% in that field (21). The generalizability of this result to medicine is uncertain, but the problems of non-replicability and false positives are not.

The second problem plaguing critical care research is a spate of negative trials of what were thought to be promising therapies. One possible explanation is that these negative trials represent "true negatives" and the trialed therapies do not work, for myriad reasons: unknown or redundant causal pathways to the outcome of interest (22), multiplicity of effects of the active treatment (pleiotropic and "off-target" effects), time dependency of causal pathways (23), etc. A second possibility is that some of the therapies are efficacious but for an outcome that was not assigned as the primary outcome (24) or was not measured at all. A third possibility is that the negative trials represent "false negatives" (16). False negative trials can result from inadequate assigned study power (25), from subversion of power calculations by delta inflation (use of an overly optimistic effect size in sample size calculations) (26), from inadequate dosing of active treatment causing failure of separation (27), or from dilution of effective sample size by patients unlikely to benefit because of severity of illness (too high or too low) (28,29) or because of heterogeneity introduced by non-specific disease definitions (30-33).

In a recent article (34), Goligher *et al*. propose one possible solution to the specific problem of false negative trials due to dilution of effective sample sizes. They reason that, prior to enrollment in a trial testing a physiological intervention for ARDS such as different doses of PEEP, a "test dose" of PEEP could be applied to prospective enrollees to determine PEEP responsiveness which would be an inclusion criterion for enrolment in the trial. By excluding patients who do not respond to PEEP with an increase in P/F ratio by a pre-specified margin, this strategy may exclude patients such as those with milder lung injury who cannot benefit from PEEP or those with severe disease and little recruitable lung who may be harmed by it (35). If this reasoning is correct, many fewer patients would need to be screened and enrolled to satisfy sample size requirements for such a trial.

The authors of this article are to be commended for scrutinizing the orthodoxy of contemporary trial design in light of its frequent failings and for proposing a possible solution. As the authors point out, for their strategy to

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work, the effect of PEEP on the outcome measure for the test dose (P/F ratio increase) must be an accurate predictor of the effect of PEEP on the primary outcome of the trial. That is to say, this strategy involves multiple bets (as do all trials in the assignment of enrollment criteria). If the predictive validity of the screening outcome for the primary outcome is imperfect, we will have excluded otherwise eligible patients with this procedure. Unanswered questions include whether informed consent will be required prior to test dose administration, and what other diseases besides ARDS will lend themselves to screening with physiological responsiveness. For example, in a trial of vasopressors for shock, would we be content to administer a test dose of levophed and exclude from enrolment patients who did not have an increase in mean arterial pressure of a given amount? Is it possible that physiological responsiveness is dynamic and that failure to respond at one time does not predict failure to respond over the course of the illness?

While screening with physiological responsiveness is seductive for its potential to reduce sample size requirements, it ignores and potentially perpetuates larger problems in our current paradigms for evidence generation in critical care medicine. The exclusion of patients unlikely to benefit provides justification for using a larger delta value in power calculations. As there is no precedent in modern critical care for a reduction in short term proportional absolute mortality of 8–11% as the authors propose in Table 1, these values are likely to be overly optimistic and thus to represent delta inflation (26). Indeed, an emerging trend in critical care trials is to enroll not fewer but more patients, increasing the statistical precision of the results which better allows clinicians to exclude clinically meaningful effects outside the resulting 95% confidence intervals (36,37). The use of mortality as a universal primary endpoint for two decades without any consistent success in RCTs should lead us to reevaluate the suitability of this metric for the achievement of our goals. Other suggested measures include QALYs and composite outcomes (24,38) that include chronic encumbrances of critical illness such as artificial nutrition, supplemental oxygen, renal replacement therapy, and need for devices to assist with walking as components. Measurement of patient-centered outcomes such as these may inform not only our choices of outcomes in future trials if we see "signal" in an individual outcome, but will also help us refocus our attention on survivors of critical illness.

We have learned much in the modern era of critical care research. Our negative results should not discourage us, especially in light of data that outcomes in practice are improving in spite of them (39). Progress and future successes will depend not only on persistence and perseverance, but also on our willingness to challenge existing paradigms and dogma. Goligher *et al*. have taken us one step farther in the direction of progress.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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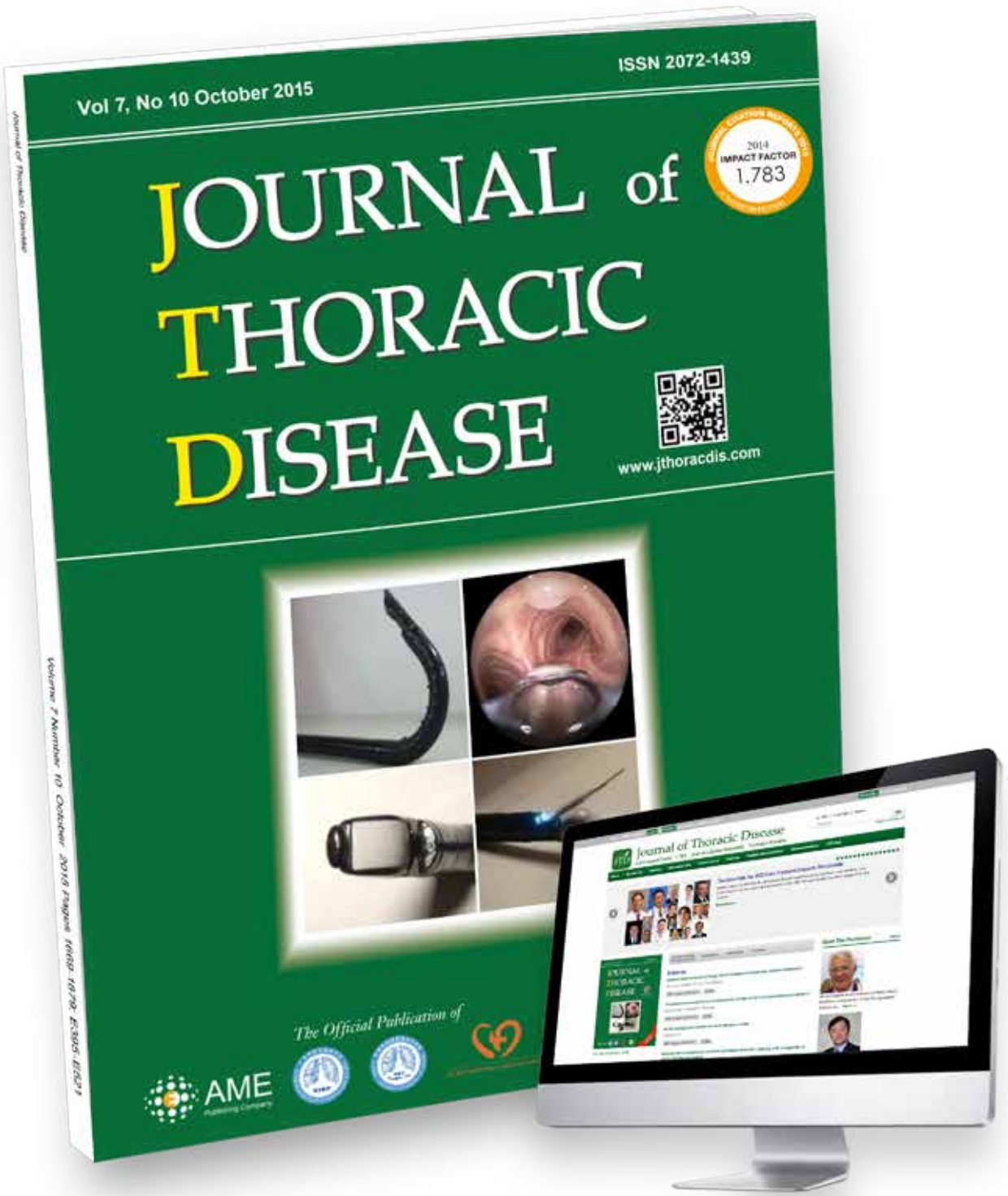
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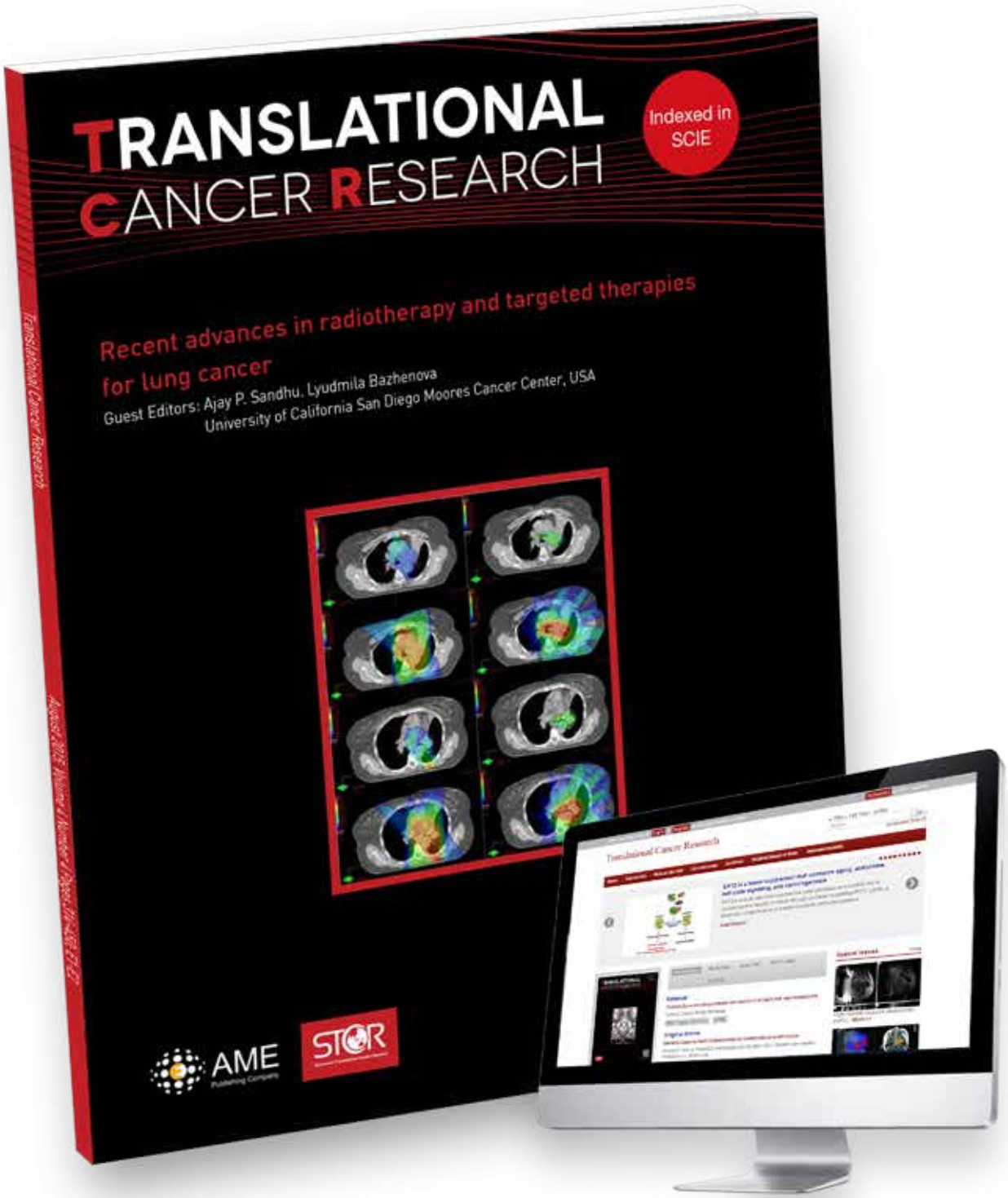
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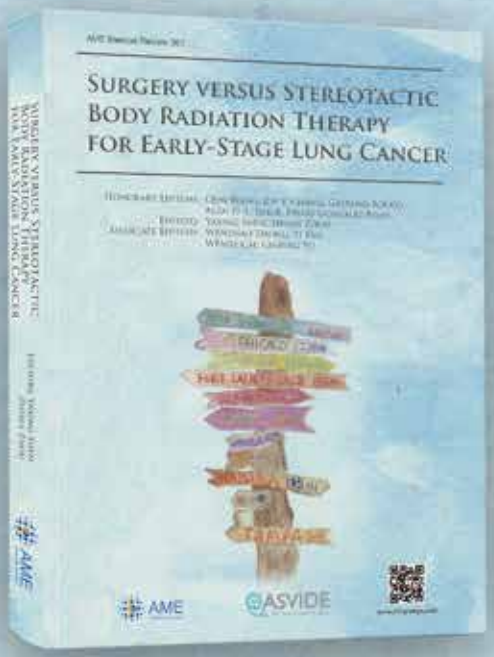

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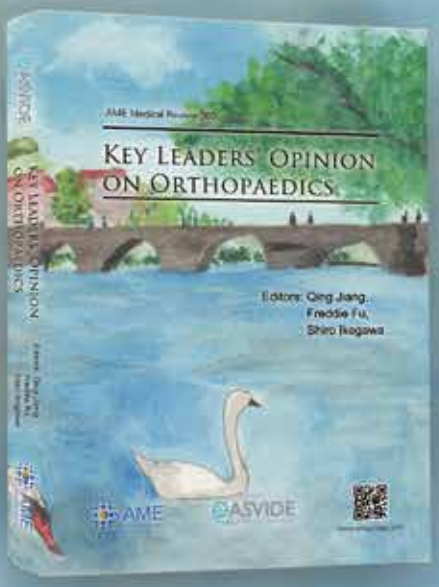

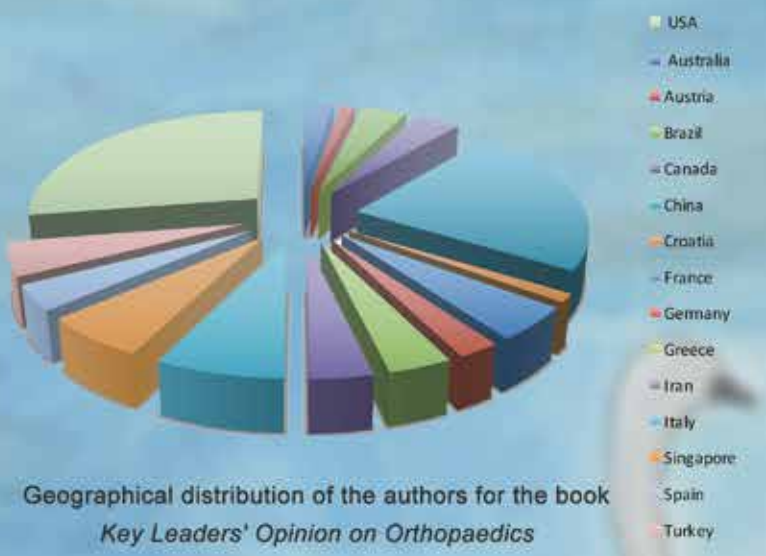

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