ICU

MANAGEMENT & PRACTICE

THE OFFICIAL MANAGEMENT JOURNAL OF ISICEM

VOLUME 17 - ISSUE 1 - SPRING 2017

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Caring for the Critically Ill Patient: Novel Strategies Optimizing Blood, Oxygen and Fluids

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Presenters

Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit - The Oxygen-ICU Randomized Clinical Trial

Massimo Girardis, MD

Professor of Anesthesiology and Intensive Care,
Head of the Department of Anesthesiology and Intensive Care Unit
University Hospital of Modena
Modena, Italy

The Evolving Role of Cardiorespiratory Monitoring: Importance of Oxygen Delivery in Acutely Ill Patients

Jean-Louis Vincent, MD, PhD

Professor of Intensive Care Medicine (Université Libre de Bruxelles)
Department of Intensive Care, Erasme University Hospital
Brussels, Belgium
President, World Federation of Intensive and Critical Care Societies (WFSICCM)

Latest Hemodynamic Strategies - Blood, Oxygen and Fluids: Friends or Foes?

Aryeh Shander, MD, FCCM, FCCP

Chief Department of Anesthesiology
Pain Management and Hyperbaric Medicine
Englewood Hospital and Medical Center
Clinical Professor of Anesthesiology
Mount Sinai School of Medicine
Mount Sinai Hospital, New York

The Noninvasive Multi-Parametric Evaluation of The Critically Ill Patient

Azriel Perel, MD

Professor of Anesthesiology and Intensive Care
Sheba Medical Center, Tel Aviv University
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LOCATION

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SESSION TIME

Tue	15:00 - 16:30
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Thu	10:30 - 12:00, 12:30 - 14:00, 15:00 - 16:30
Fri	10:30 - 12:00

Personalised/ Precision Medicine

The progress towards, and potential of, personalised/ precision medicine in intensive care is the theme for our cover story. We are making progress in moving away from therapies based on poorly characterised patient populations to more personalised treatment of critically ill patients, although true precision medicine, based on individual genes, environment and so on lies some way in the future. Andrew Prout and Sachin Yende discuss the challenges of precision medicine in sepsis and suggest potential implementation strategies. Ignacio Martin-Loeches, Lieuwe Bos and J. Perren Cobb consider precision medicine for acute respiratory distress syndrome, and suggest that in the post-genomic era, precision medicine is more likely to provide the next big advances in ARDS diagnosis, treatment and outcomes.

The World Health Organization recently issued its first global priority list of antibiotic-resistant bacteria (**https://iii.hm/8xt**). This follows the 2013 publication of a similar list by the U.S. Centers for Disease Control and Prevention. It is certainly time to take antimicrobial resistance seriously, as Jan de Waele argues in the first article in the Matrix section this issue. While data on the scale of the problem in ICUs is limited, the ICU team needs to do all it can to ensure appropriateness of antibiotic therapy in patients with infections due to multidrug resistant (MDR) pathogens while minimising antibiotic exposure in all ICU patients in the ICU, he argues. Next, Jeroen Schouten describes a stepwise approach to implementing antimicrobial stewardship in the ICU. He advises starting with the basics, targeting one problem at a time, and taking a structured approach with the Plan-Do-Study-Act cycle.

Fabienne D. Simonis, Marcus J. Schultz and Antonio Artigas discuss the evidence on the benefit of protective ventilation strategies in patients without ARDS, including the use of low tidal volumes, higher levels of PEEP and lower driving pressure levels. They look forward to the results of several ongoing randomised controlled trials.

Next, Giuseppe Citerio puts the case for quantitative EEG in the ICU. It's both useful and feasible, he says, and he describes how it was implemented in his neurointensive care unit, supported by a neurophysiologist. Continuing in neurocritical care, Timothée Abaziou and Thomas Geeraerts explain the use of brain ultrasound as a promising tool to visualise most of the intracranial structures, allowing estimation of risk posed by life-threatening conditions.

In the late 1990s, albumin came under fire for increasing mortality in critically ill patients, and use declined in many countries. Neil J. Glassford and Rinaldo Bellomo outline the case for and against albumin administration in sepsis, concluding that clinical judgement and physiological reasoning, rather than strength of evidence, are still the primary drivers for the administration of albumin in critically ill patients.

Our Management section begins with an article on the patient perspective, from Julie Vermeir and Darryl O'Callaghan, who describe their 'virtual Everest'—the journey they took as husband and wife after Darryl was critically injured in a road accident. They now use that experience as consumer representatives in a large hospital.

Human factors specialists can make healthcare safer for both staff and patients in many ways, as explained by Svetlena Metzger. Their roles can include mitigating risks, investigating incidents, testing equipment and re-designing processes. Next, Fiona Coyer and Jeff Lipman outline the establishment of a Intensive Care Nursing Professorial Unit, which aims to build an active research culture and support intensive care nurses in evidence-based practice.

Even in the 19th century, Florence Nightingale observed the beneficial effects of music on patients. Former ICU patient, Helen Ashley Taylor, describes a project from Music in Hospitals™, which brings professional musicians into the ICU.

Patient safety expert, Peter Pronovost, is interviewed for this issue. We asked him to share his thoughts on progress on safety since the publication of *To Err is Human*, what the ICU of the future should be like, and much more.

China is the subject of our Country Focus. Bin Du summarises the state of intensive care medicine in this vast country—as a discipline it was relatively recently recognised as a specialty, and postgraduate education and more participation in research is needed, he says.

The *ICU Management & Practice* team will be at the International Symposium on Intensive Care & Emergency Medicine (ISICEM), which meets for the 37th time this month in Brussels. Hope to see you there

As always, if you would like to get in touch, please email **JLVincent@icu-management.org**

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COVER STORY

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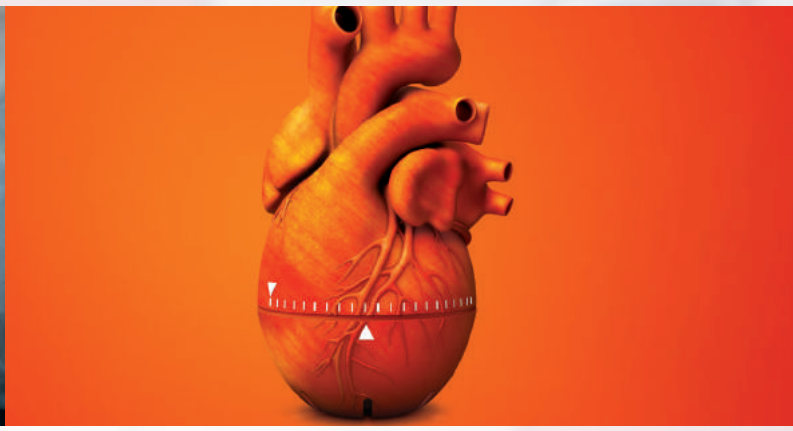

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BALANCE

Consequences of unbalanced sedation
Björn Weiss (Germany)*

How dexmedetomidine gets the 3Cs right
Robert Sladen (US)

TIME

Inotropy without increase in oxygen consumption
Fabio Guarracino (Italy)

Long-lasting effects of levosimendan
Dominique Bettex (Switzerland)

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Welcome!

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ORION PHARMA

The AKIpredictor

An Online Calculator to Predict Acute Kidney Injury

Marine Flechet
PhD student

Geert Meyfroidt
Associate Professor of Medicine
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University Hospitals Leuven
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Acute kidney injury (AKI), a rapid decline in renal function, is highly prevalent in critically ill patients, and is associated with an increased risk of short- and long-term complications that extend beyond the acute phase (Pickkers et al. 2017). AKI is defined and classified by an increase in serum creatinine or a decline in urine output, both late and non-specific markers of the underlying phenomenon. There is no cure for established AKI, and its management in the intensive care unit (ICU) consists of optimisation of fluid status and blood pressure, avoiding nephrotoxic agents, and the use of renal replacement therapy. Early detection of subclinical AKI could allow for preventive measures, for earlier or more directed therapy, or for a better stratification of patients to design new therapies or interventions that could mitigate the course of AKI. The role of early biomarkers of structural kidney damage, such as neutrophil gelatinase-associated lipocalin (NGAL), or the combination insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteases 2 (IGFBP7/TIMP2) to guide AKI management is currently unclear. Biomarkers are expensive, and the subgroups of patients that would benefit most from follow-up with biomarkers have yet to be identified.

> **AKIpredictor has the potential of becoming a rapid screening tool for critically ill patients**

We have developed clinical prediction models for AKI, based on routinely collected patient data (Flechet et al. 2017). The models have been developed and validated in a large multicentre database, using a random forest machine-learning algorithm, which makes optimal use of all data. They have been made available for free as an online calculator (http://akipredictor.com) The AKIpredictor calculates the risk of developing AKI within the first week of ICU stay, for critically ill patients in the early stages of their ICU course, as clinical information becomes available: before admission, upon admission and after the first day. The performance of the models was excellent, and we were able to demonstrate that the ICU admission model outperformed serum NGAL, but also that the model could be combined with the biomarker.

The AKIpredictor has the potential of becoming a rapid screening tool for critically ill patients, because it is cheap, accurate, and does not require additional data beyond what is already collected routinely. We hope that online access to the AKIpredictor will encourage research groups to collaborate with us, to improve, and to further validate the models. Obviously, the potential clinical benefit of this tool still needs to be demonstrated. Early risk assessment could be key to detect subgroups of patients that might benefit from certain interventions, to be included in clinical trials, or to select higher-risk patients who might benefit from additional follow-up with new biomarkers such as IGFBP7/TIMP2, especially if combining them would boost the predictive performance of both. As such, the AKIpredictor could be a useful aid for tailored stratification of patients, and maybe a step towards personalised medicine for AKI. ■

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Surviving Sepsis Campaign 2016 Guidelines Released

The Surviving Sepsis Campaign (SSC) (**survivingsepsis.org**), has released its 2016 guidelines for the management of sepsis and septic shock. The document, published simultaneously in Critical Care Medicine and Intensive Care Medicine, is an update to the 2012 SSC guidelines.

The recommendations in the document cannot replace the clinician's decision-making capability when presented with a patient's unique set of clinical variables, according to the international consensus committee, composed of 55 international experts representing 25 international organisations involved in the care of patients with sepsis. Unlike most clinical guidelines that contain a "what to do" list, the updated SSC guidelines also include many recommendations that are negative or "what not to do".

Committee member, Prof. Jean-Louis Vincent, MD, PhD, FCCM, of Erasme University Hospital, Brussels, explained why to *ICU Management & Practice*.

"Our committee wanted to strictly limit recommendations to what is well established in the literature (so-called evidence-based) and virtually all our clinical trials in the field have been negative or have shown harm rather than benefit. Hence it is not surprising that most recommendations are negative, i.e., indicating what we should not do rather than what we should do. Guidelines are helpful to guide those who do not follow the literature and this updated version will be welcomed by non-experts."

Fellow committee member, Prof. Flavia Machado, of the Latin America Sepsis Institute, told *ICU Management & Practice*: "The Surviving Sepsis Guidelines 2016 bring new perspectives on sepsis treatment. The recommendations are all based on the best available evidence, also taking into account not only the balance between costs and benefits but also the feasibility and the economic impact. This is of major relevance for the low and middle-income countries where resources are limited and need to be carefully directed to those who could really benefit from them." ■

Reference

The guidelines and related resources are linked on the Surviving Sepsis Campaign website at survivingsepsis.org/Guidelines/Pages/default.aspx

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Personalised Medicine in Intensive Care

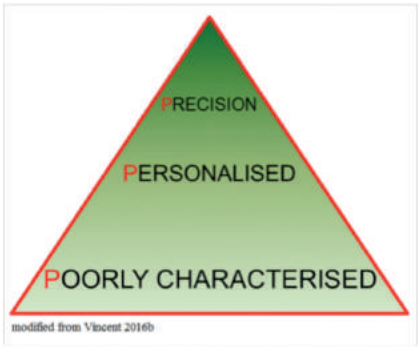
The specialty of intensive care medicine grew out of the realisation that critically ill patients needed more attention and specialised treatment than could be provided on a general ward, and that many of these patients had similar clinical problems and processes, so management would be facilitated if they were grouped together in one place. Since those early days, intensive care medicine has grown rapidly with major advances in technology and understanding of disease pathogenesis and physiology. Progress in therapeutic interventions has, however, been less marked. One of the reasons behind the lack of effective new therapies relates to problems in performing randomised clinical trials in the very heterogeneous ICU patient populations. Indeed, since the birth of intensive care medicine, we have tended to group patients with similar signs and symptoms together under "umbrella" diagnoses, such as "sepsis", "acute respiratory distress syndrome", "acute renal failure", ignoring the considerable heterogeneity within these groups in terms of individual characteristics, such as age, comorbid conditions, and genetic predisposition to disease; disease severity and degree of immune response; and individual variations in response to treatment. Performing randomised controlled trials in such mixed groups of patients will almost inevitably result in an inconclusive result as some patients in each group will respond to the therapy and others will not (Vincent 2016a).

Indeed we are increasingly aware that on the ICU, as across all other medical fields, patients must be treated as individuals and not as diseases. We have perhaps been too concerned with defining syndromes and diseases and have somewhat "forgotten" the individual people behind those conditions. We commonly hear phrases such as "he's septic", "she's a diabetic", "where's the ARDS patient?", encouraging this attitude of defining patients by their diagnoses, but we need to look behind the group label and see the individual patient so that we can select the most appropriate treatment for that person at that moment in time. This personalised approach to medicine is not new; indeed, more than 2400 years ago, Hippocrates had already noted the importance of individual characteristics in the development and progress of disease and evaluated each patient and adjusted treatment according to their "constitution, age, physique, the season of the year, and the fashion of the disease" (*Hippocrates, Nature of Man*). Basic vital signs and variations in physiological parameters, such as body temperature, heart rate and respiratory rate, have also been used for centuries to assess a patient's response to therapy. As medicine has progressed, increasingly more complex parameters have been used to predict outcome and adjust therapy, such as blood pressure and cardiac output. In another attempt to help characterise patients, biomarkers have been developed and studied as potential risk, diagnostic and prognostic indicators for various conditions, including sepsis and acute kidney injury (AKI) (McMahon and Koyner 2016; Pierrakos and Vincent 2010) although problems of specificity and availability have limited their widespread use.

> "patients must be treated as individuals and not as diseases"

These relatively non-specific and simple methods are now being complemented by more advanced techniques as, with the huge technological advances of the last decade or so, we have begun to enter a whole new era of personalised medicine. Genomic, transcriptomic, proteomic, and metabolomic profiling techniques are enabling patients' risks of disease and likely response to treatment to be more closely identified, such that the treatment(s) most likely to benefit that patient can be selected. For example, using genomic expression profiling, Wong et al. (2015) identified two subgroups of children with septic shock, one of which had increased mortality when prescribed corticosteroids. Similarly, using whole genome amplification on blood samples from patients included in the PROWESS study (Bernard et al. 2001), Man et al. (2013) identified two subgroups of patients with different responses to treatment with drotrecogin alfa (activated). The personalised medicine approach is now being applied to clinical trials, helping select more specific groups of patients who are most likely to respond to an intervention rather than the heterogeneous populations of the past. For example, a study comparing granulocyte-macrophage colony-stimulating factor (GM-CSF), an immunostimulating drug, with placebo, is currently ongoing in patients with sepsis, but enrolling only patients identified as being immunosuppressed based on their human leucocyte antigen (HLA)-DR level (clinicaltrials.gov/ct2/show/NCT02361528) Such studies will help, finally, to identify new therapies and interventions for conditions, such as sepsis, in which multiple clinical trials in heterogeneous patients groups have so far failed. Importantly, as these 'omic techniques become more widely used, costs will decrease. Drug development prices may also decrease as study populations are more carefully defined, making trials more efficient.

Hand in hand with new analytic technology has come improved informatics



capability, enabling sophisticated analysis of the large sets of patient data (demographic, physiological, laboratory and new 'omic data) being collected, aided by national and international collaborations. Simulated models are also being developed to test suggested interventions on "virtual" patients or groups of patients, informing drug development and clinical trial design. The integration of all these data into "supermodels" (Brown 2015) may ultimately enable a physician to access a personalised treatment plan for every individual. These intelligent models will be able to update and adjust recommendations automatically as new data are received.

Clearly, this is still a somewhat futuristic view of personalised medicine in the ICU. Nevertheless, as we are increasingly able to better characterise patients, our ability to identify subgroups within subgroups will increase until we reach the point at which each subgroup consists of just one patient (Gattinoni et al. 2016). This will be true precision medicine, in which medical treatments will be customised to an individual's molecular and genetic makeup. Although this approach is already being used in oncology, in the ICU environment, with the very rapid changes that occur in patient status, requiring regular treatment adjustment and thus necessitating repeated phenotypic profiling, true precision medicine is still some way off. Nevertheless, the progress from poorly characterised patient groups to personalised medicine is already a huge advance (Vincent 2016b). ■

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Precision Medicine in Sepsis

Multiple failed clinical trials testing immunomodulatory therapies for sepsis argue for a new approach. While precision medicine has been successfully implemented in other fields, testing it in sepsis poses challenges, which this review will discuss, along with potential implementation strategies.

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Sepsis has an estimated annual incidence of 1.3 million cases and 230,000 deaths (Stoller et al. 2016). Short-term mortality has declined in the adult population from approximately 40% to 20% from 2001 to 2010 (Gaieski et al. 2013). Short-term mortality of neonatal and paediatric patients with sepsis has had a similar decline, from 20% to 10% (Balamuth et al. 2014) in the corresponding time period. Despite a decline in early mortality, survivors of sepsis hospitalisation continue to incur multiple long-term effects, including increased risk of mortality and morbidity (Yende and Iwashyna 2012; Prescott et al. 2014; Mayr et al. 2014).

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Significant advancement has been made in understanding the pathogenesis of sepsis and septic shock at the molecular and cellular level in the past 20 years using preclinical and in vitro models. Many potential therapies have shown promise in preclinical models and hundreds of therapies have been tested in randomised clinical trials (RCTs) in humans. However, none, with the possible exception of glucocorticoids, have consistently shown improvement in mortality. Subsequently, there are no immunomodulatory therapies currently approved by the U.S. Food and Drug Administration for sepsis. This review focuses on the role of precision medicine to develop strategies to modulate the immune response to improve outcomes in sepsis.

Why Test a Precision Medicine Approach for Sepsis?

There are several potential reasons for the failure of immunomodulatory therapies in human trials. These include difficulty in extrapolating findings in animal models to patients with multiple co-morbidities, and the need to consider patient heterogeneity. It is likely that many of the immunomodulatory therapies tested to date may be beneficial for some patients, but they have not been targeted to the right patient at the right time.

> "sepsis frequently causes differential endotypes in the same patient over time"

Precision medicine, as currently understood, attempts to integrate clinical phenotype with patient genetic and molecular data to define a subgroup of patients that may benefit from a particular therapy. This subclassification integrates clinical, genetic and pathobiological data with treatment response to classify distinct disease endotypes (Anderson 2008). Within pulmonology, recent efforts have focused on defining endotypes within asthma, with some success in defining distinct treatment response patterns (Lötvall et al. 2011; Fajt and Wenzel 2014). Precision medicine has also been successfully implemented in oncology. Clinical trials and treatment protocols in oncology often use advanced molecular, genetic, and biomarker data (Kaufman 2014), with significant improvement in outcomes of melanoma and breast cancer. Within critical care, investigators have also classified acute respiratory distress syndrome into two distinct endotypes with different clinical and inflammatory biomarker profiles. These endotypes have differential responsiveness to positive end-expiratory pressure (PEEP) (Calfee et al. 2014) and different fluid management strategies (Famous et al. 2016) in retrospective analyses of clinical trials.

Early Efforts to Test Precision Medicine in Sepsis

Prior trials of targeted therapy in sepsis have defined an altered molecular pathway and evaluated the efficacy of a molecule that is known to resolve that alteration in preclinical models. The majority of RCTs that have been performed for sepsis therapies to date have enrolled a broad group of patients with sepsis, or narrowed enrollment to a subgroup of patients based on the degree of organ failure or presence of septic shock. However, only a few trials have attempted to test immunomodulatory therapies based on biomarker profiles. The Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial, a multicentre trial (n=2,634) of an anti-tumour necrosis factor (TNF) $F(ab')_2$ monoclonal antibody, randomised all patients to treatment or placebo, but pre-specified that patients with a presumed hyperinflammatory phenotype, defined by elevated circulating interleukin (IL)-6 levels, would benefit from anti-TNF therapy. The trial did find a mortality benefit in the overall analysis, but the benefit was not statistically significantly different in patients with elevated IL-6 levels (Panacek et al. 2004). Meisel et al. conducted a multicentre RCT

(n=38) and tested GM-CSF in patients who were immunosuppressed, as evidenced by low HLA-DR expression on monocytes (Meisel et al. 2009), and showed an improvement in HLA-DR expression, ex vivo TLR response, intensive care unit length of stay and mechanical ventilation duration. The Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES) trial (Klein et al. 2014) is ongoing and is testing the anti-endotoxin strategy, polymyxin haemoperfusion, in 360 patients who had endotoxaemia at enrollment.

There have been several post hoc analyses of failed sepsis trials that have identified potential sepsis endotypes. For example, a post hoc analysis of a phase III trial of anakinra, an IL-1 receptor antagonist, stratified patients with clinical features of macrophage activation syndrome (MAS), including hepatobiliary dysfunction and disseminated intravascular coagulation, and found a significant survival benefit in this subgroup of patients (Shakoory et al. 2016; Opal et al. 1997). Another approach is to identify endotypes in observational studies. For instance, in paediatric patients with septic shock, Wong and colleagues defined endotypes of patients based on multiplex gene analysis. They found that patients who expressed one of the endotypes had improved outcomes with glucocorticoid treatment (Wong et al. 2016). Proof-of-concept clinical trials showing that a precision medicine approach would be successful in sepsis are lacking.

Barriers to Implementing Precision Medicine in Sepsis

There are several important differences between chronic diseases, such as cancer and asthma, and acute conditions, such as sepsis. Endotypes have to be identified within hours in sepsis, in contrast to chronic diseases, where endotypes could be identified over days or weeks. This rapidly evolving time course of critical illness renders use of potentially advanced diagnostic strategies, such as gene-expression microarray, of limited utility. While this remains a significant barrier, progress has been made in more rapidly testing and defining endotypes with Nanostring technology, which has been implemented successfully in retrospective analyses (Wong et al. 2015; Cuenca et al. 2013), but remains challenging to implement in a prospective fashion.

In conjunction with the need to measure biomarkers rapidly, sepsis frequently causes differential endotypes in the same patient over time, exemplified by the well-recognised immunosuppression following the initial exaggerated inflammatory state. This inter-patient endotypic variation has been postulated as one underlying mechanism for the failure of clinical trials in sepsis (Marshall 2014; Iskander et al. 2013; Cohen et al. 2015).

Pathogenic mutations in oncologic processes are often specifically maladaptive, and complete inhibition is feasible and may not be harmful. In contrast the pathologic host response in sepsis is multifaceted and multidirectional, and modulation of a molecule or a pathway may have deleterious effects. For example, restoration of immunosuppression in septic patients may increase the risk of acute respiratory distress syndrome. Similarly, prolonged

inhibition of a pathway may worsen immunosuppression and increase the risk of secondary infections.

Potential Approaches to Implementing Precision Medicine

Precision medicine cannot work unless drug-response or treatment-response phenotypes are properly identified. Many investigators have used biomarkers to identify patient groups who are more or less likely to have bad outcomes (prognostic markers), but not those more or less likely to respond to a therapy (predictive markers). This distinction is critical. For example, the high IL-6 group in MONARCS had a higher mortality rate, but no difference in drug response (Panacek et al. 2004). Outcome phenotypes are far easier to discover, and can potentially be identified in any observational cohort. In contrast, drug-response phenotypes are most readily determined through interrogation of an observational cohort or secondary analyses of a RCT by examining an interaction between the treatment and the phenotype. Identifying drug-response phenotypes is important. If these phenotypes are not correctly identified, investigators may narrow enrollment in a clinical trial to the wrong group.

These endotypes can be identified by measuring genomic, proteomic and microbiome markers in large observational cohorts. The electronic health record can be leveraged to efficiently identify such endotypes (e.g., BioVu **victr.vanderbilt.edu/pub/biovu**). Using big data will require harmonisation of data across multiple sites and replication of these endotypes in multiple data sets. Novel statistical methods, including latent class analysis, machine learning and principal components analysis will be necessary. However, a key limitation of relying only on observational studies is that results could be confounded. Replicating results in secondary analyses of clinical trials would be important to validate these endotypes, though such data sets are not routinely available.

The results of observational studies described above should be used to optimise the design of clinical trials. If endotypes are not readily available or multiple endotypes are identified, adaptive trials could be used. These trials could enrol and randomise patients across multiple endotypes. As different groups of patients progress through the trial, their response to interventions in different biomarker-defined groups triggers, via pre-specified Bayesian models, adaptations in the randomisation scheme (response-adaptive randomisation). These rules allow the trial to reduce exposure of patient subgroups that may be harmed by the treatment and improve trial efficiency. For example, the I-SPY2 trial for breast cancer used a remarkably small sample size to test 7 regimens in 8 biomarker-defined groups (Barker et al. 2009; Park et al. 2016).

Conclusion

While the implementation of precision medicine in sepsis will be difficult, it is apparent that the current paradigm for novel therapeutic sepsis trials has been insufficient to address the heterogeneity of this disease. It is not clear that precision medicine will lead to better outcomes, but success in other fields, such as oncology, argues for abandoning the one-size-fits-all approach and testing a more targeted approach. Critically ill patients with sepsis represent a unique challenge for precision medicine. Rapidly evolving pathophysiology, multisystem organ failure and high mortality risk combine to make successful precision medicine difficult to operationalise. However, the lack of progress and significant persistent burden of disease highlight the importance of improving clinical trial design and care of this persistent and deadly disease.

Acknowledgements

This work was supported by grants R01GM097471 and R34GM107650 from the National Institute of General Medical Sciences.

Conflict of Interest

Andrew Prout declares that he has no conflict of interest. Sachin Yende declares that he has no conflict of interest. ■

Abbreviations

RCT randomised controlled trial

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ARDS and Precision Medicine

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What is the path forward for treatment of acute respiratory distress syndrome (ARDS)? Is it big trials (favoured by clinical scientists) or further insight into disease physiopathology (favoured by basic scientists)? Or both? Funding resources are limited and the debate is wide open. In the post-genomic era, a new direction is needed. On 20 January 2015, then U.S. President Barack Obama announced the Precision Medicine Initiative® (PMI), the main focus of which is a clear call for a more organised, systematic approach for disease treatment and prevention that takes into account individual variability in environment and genetics for each person (**obamawhitehouse.archives.gov/precision-medicine**).

Precision medicine is a promising strategy for many complex diseases that have proven difficult to prevent or treat using a population approach. This is especially true for intensive care medicine, where syndromic diagnoses are common and randomised controlled trials frequently include heterogeneous patient populations (Vincent et al. 2016). For example, many recent clinical studies in intensive care units erred on the side of large sample sizes, ignoring heterogeneity in the selected study population for lack of accurate molecular biomarkers. Promising therapeutic approaches might have harmed as many patients as they helped. ARDS is arguably one of the most poorly characterised diseases in intensive care units (ICUs) (Sheu et al. 2010). We frequently deal with the dilemma that the patients we treat in our ICUs may or may not reflect the syndrome diagnosis that is used to include patients in clinical trials.

For decades, there was no common definition for ARDS, which resulted in a very wide range of reported prevalence. In 1994 the American-European Consensus Conference (AECC) definition became globally accepted and addressed some of the problems of clinical characterisation. In the AECC definition ARDS was graded based on oxygenation relative to the fraction of inspired O_2 (PaO_2/FiO_2) (Bernard et al. 1994; Artigas et al. 1998). Treatment bundles fostering what became known as "protective lung ventilation" were the most important achievements that followed. Difficulties in interpretation of chest radiography and the lack of a standardised positive end-expiratory pressure (PEEP) level, however, limited the application and utility of the AECC definition. In 2012 the new Berlin Definition of ARDS was established to solve the aforementioned limitations. This definition improved the interpretation of the chest radiograph and established a minimum level of PEEP (Costa and Amato 2013; ARDS Definition Task Force 2012). Despite these improvements, the definition still lacks differentiation based on underlying aetiology, a direct measure of lung injury, and markers that identify early patients who may benefit from preventive therapies (Bellani et al. 2012). Another unresolved conundrum is the lack of agreement between ARDS and lung histology. One would hope that pathological studies would help better characterise the disease and therefore improve clinical phenotyping. Yet Thille et al. found (Thille et al. 2013a; 2013b) that in 712 autopsies analysed 356 patients had pathological criteria for ARDS at the time of death, showing a very poor specificity (63%) in identifying ARDS using the Berlin Definition. Moreover, diffuse alveolar damage (DAD) at autopsy was found in less than half of the patients with clinical criteria for ARDS (Guerin 2011). The limitations of the Berlin Definition largely reflect the limitations of clinical characterisation. Ultimately, this lack of agreement with lung pathology will ultimately impact in less-than-optimal customisation of the patient's care, incongruent with the goals of precision medicine (decisions, practices, and/or products being tailored to the individual patient).

We, therefore, need to consider introducing new tools to better characterise ARDS. Currently available bedside diagnostic tools should be evaluated in clinical studies and if they have added value implemented in daily clinical practice. One of the challenges is that a novel diagnostic test for lung injury would be applied using the Berlin Definition, which fails for the reasons described above as a "gold standard" for classification. Thus, clinical trials should be constructed to test a regimen of novel diagnostics as compared to standard clinical diagnostics for prediction of successful treatment intervention.

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Patient selection for trials should also be tested based on physiological parameters that measure the underlying pathophysiology. For example, tools such as electrical impedance tomography and thermodilution-estimated extravascular lung water (EVLW) might provide better insight into the physiopathology and therefore direct a more individualised treatment approach. ARDS is defined by a histopathology pattern of diffuse alveolar damage and correlated with an increased EVLW, which can be measured at the bedside by the trans-pulmonary single-indicator thermo-dilution method. EVLW should be tested as a diagnostic criterion for ARDS, and might easily predict disease severity and outcome, adding value as a diagnostic criterion of ARDS (Camporota et al. 2012).

Another method for the bedside monitoring of lung pathophysiological processes is the analyses of exhaled breath (Nseir et al. 2011). Breath contains hundreds of volatile organic compounds that are produced during normal metabolism of the host, bacterial metabolism, or as a result of lipid peroxidation during an inflammatory response (Bos et al. 2014a). The octane concentration in exhaled breath was shown to be higher in patients with ARDS. This molecule is linked to peroxidation of oleic acid (Bos et al. 2014b). Both lipid peroxidation and oleic acid have been implicated in the pathogenesis of ARDS. Additionally, ethylene, another compound associated with the peroxidation of oleic acid, significantly increased during periods of oxidative stress in cardiac surgery. These two observations combined suggest that breath analysis might be used to evaluate lipid peroxidation in patients with ARDS (Boots et al. 2015). Because exhaled breath is available continuously for rapid analysis in mechanically ventilated patients, this approach might be useful as a continuous assessment of the pathophysiological process that is central to the development of ARDS.

Finally, another approach to test is a "mixed model" of ARDS classification which relies on phenotyping based on clinical characteristics, causes of lung injury, and/or individual or sets of biomarkers (Calfee et al. 2015). Since there is considerable heterogeneity between patients with ARDS, some patients might benefit from an intervention that harms others (Papazin et al. 2016). Stratification on biological responses to lung injury (i.e., the biological phenotype) may allow for better selection of patients for a certain intervention, allowing exclusion of patients that have a low chance of benefit (or even harm) (Beitler et al. 2016). Measuring a wide range of markers in a group of ARDS patients and clustering those patients together that have a similar biological profile could help identify biological phenotypes (Calfee et al. 2014). In a post-hoc analysis of two randomised controlled trials, this approach identified two groups of patients that respond differently to increased PEEP and fluid therapy. We believe that these biological phenotypes might also be used in future studies to target immunomodulatory treatment (Beitler et al. 2016).

Conclusion

While big clinical trials of ARDS have provided important treatment benefits over the last two decades, precision medicine in the post-genomic era, based on novel molecular diagnostics and better phenotyping, is more likely to provide the next big advances in ARDS diagnosis, treatment and outcomes. ■

Conflict of Interest

Ignacio Martin-Loeches declares that he has no conflict of interest. Lieuwe Bos declares that he has no conflict of interest. J. Perren Cobb declares that he has no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome
EVLW extravascular lung water
PEEP positive end-expiratory pressure

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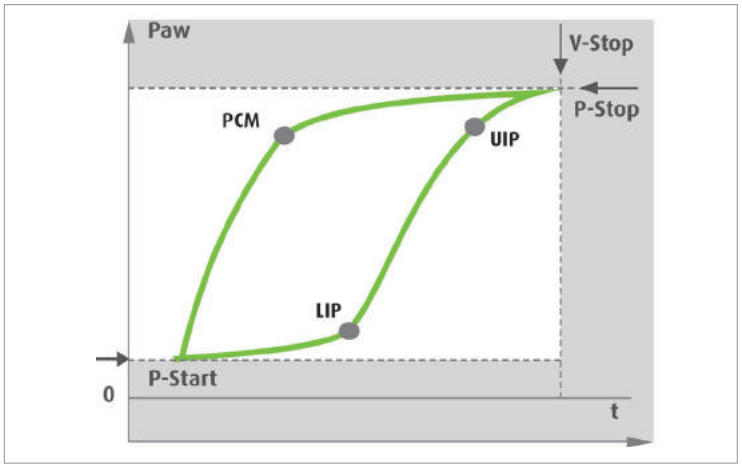

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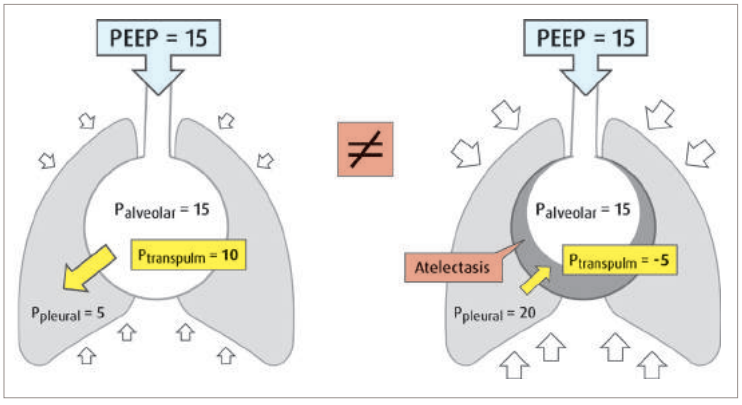

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Mechanical ventilation has become the established standard therapy for acute respiratory failure in modern intensive-care medicine. Although intensive-care ventilation frequently represents the only option to ensure sufficient pulmonary gas exchange and adequate tissue oxygenation, ventilation therapy can also cause further lung damage and lead to ventilation-induced lung injury (VILI).

While ventilation-induced lung injury (VILI) used to be commonly referred to as "barotrauma", new findings have led to a more nuanced understanding since the start of the new millennium. It is now known that cyclic alveolar collapse, along with atelectrauma, high tidal volumes (volutrauma) and high ventilation pressures (barotrauma) are the chief mechanisms of ventilator-associated lung injury (VALI). Further study results have demonstrated that lung-protective ventilation reduces mortality rates in patients with acute lung injury by preventing VALI.

The objective must be to recognize and treat any ventilation situation that may cause VALI as early as possible. The individual, adequate and disease-specific adjustment of ventilation therapy is therefore an essential requirement for preventing ventilator-associated lung injury. elisa800VIT offers a wide range of diagnostic tools for this purpose.

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Antibiotic Resistance in the ICU

Time to Take Things Seriously!

Multidrug resistance (MDR) is increasing worldwide and has been acknowledged as one of the major threats to healthcare by the World Economic Forum and the World Health Organization (World Health Organization 2014). Intensive care unit (ICU) patients seem to be particularly susceptible for acquiring MDR organisms, either just as colonisers, or as pathogens causing invasive infection. This increased risk is due to both patient factors as well as environmental factors such as antibiotic exposure, hospitalisation and environmental contamination with MDR bacteria (Bassetti et al. 2015a). Whereas Gram-positive pathogens were considered the major threat in the 1990s, the focus now is much more on Gram-negative micro-organisms that have developed resistance to many of our currently used antibiotics. Combined with the fact that no new antibiotic classes and only few new agents are becoming available in the near future (Harbarth et al. 2015), this offers only a grim preview on what we can expect in the next decades. A report from the Department of Health in the UK estimated that 300 million people will die over the next 35 years from MDR infections (Lancet 2014).

All critical care healthcare workers need to be aware of the problem of antimicrobial resistance (AMR) and the immediate threat associated with MDR isolates in the ICU. There are two specific challenges to intensivists when it comes to MDR: first, early identification and appropriate treatment of patients at risk as well as patients with confirmed MDR infections, and second, avoiding spread and development of antibiotic resistance to other patients. In this respect, controlling one of the major contributors to MDR development, antibiotic use, is critical. In this article, we will discuss the different aspects of treating patients with MDR infections. Appropriate antibiotic use will be covered by another article in this series (see p. 20).

Historical Perspective on Antibiotic Resistance

AMR is not a new phenomenon. In fact, it has been present ever since antibiotics were discovered (Perry et al. 2016). For all antibiotic classes, AMR was described soon after the introduction of the drugs. AMR may have been present even before antibiotics were discovered and used in clinical practice. This however does not mean that recent trends in AMR should be taken lightly and discarded as a phenomenon that is implicit to the use of antibiotics and a natural, evolutionary event. The increase in MDR infections and difficult-to-treat pathogens is happening in many ICUs worldwide.

It is also a reality, however, that the lack of susceptibility to our current antibiotics causes patients to die in the ICU, many of them primarily admitted for other reasons than infections. In others, protracted and recurrent infections—often due to inappropriate initial therapy associated with MDR infections—and prolonged antibiotic exposure, leads to increased morbidity and prolonged hospital stays.

This phenomenon is not likely to go away, but a fatalist attitude is not appropriate here either. Although the antibiotic options may be limited, adequate antibiotic treatment is possible for most infections, through an improved use of older antibiotics, as well as new agents coming to the market. While early identification is difficult, new techniques are becoming available that allow early identification of infected and colonised patients. Although infection control is tough to implement and maintain, knowledge is increasing and prevention of MDR spreading to other patients is feasible.

Defining Antimicrobial Resistance

Whereas AMR is a common occurrence, with many micro-organisms being naturally resistant against certain antibiotics, the real problem is MDR, the situation where there is acquired resistance against an increasing number of antibiotics. According to the definition proposed by an international expert panel in 2012, MDR refers to resistance to one or more antibiotics in three or more antibiotic classes. Extensive drug resistance (XDR) is defined as resistance to at least one antibiotic in all but 2 or fewer antibiotic classes, and pan-drug resistance (PDR) is defined as non-susceptibility to all agents in all antibiotic classes (Magiorakos et al. 2012). This conceptual framework can be applied to all pathogens, but is limited to the need for extensive antibiotic susceptibility testing (AST) to appropriately classify all pathogens—Gram-positive or Gram-negative. In clinical practice this detailed information is rarely available, and as a result this classification is interesting for epidemiological studies and benchmarking, but not useful at the bedside. Also the fact that resistance to only one drug in a certain antibiotic class is enough as one of the three criteria for MDR, may not reflect the real-life challenges in antibiotic selection for MDR pathogens. Therefore in many studies a more practical approach is used where often the focus is on the resistance mechanism or resulting phenotype e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacteraceae, carbapenem resistant Enterobacteraceae (CRE), MDR *Pseudomonas aeruginosa*, among others. These are also the pathogens that are most challenging to treat, and focusing on a pathogen rather than the MDR/XDR/PDR classification is probably a more rational and clinically oriented approach. There clearly is a difference in approach from a clinical perspective compared to the microbiological perspective.

Epidemiology in Critical Care

Large-scale, detailed, epidemiological data on AMR in our ICUs worldwide are scarce. Most studies in the literature are either single centre reports (often before-after studies on a particular intervention), or focus on an outbreak and the management thereof. Large-scale epidemiological data exist, but ICU-specific data are rarely available, and are mostly limited to a small number of centres contributing to the database. Moreover, there are limited longitudinal data available, so it is hard to make any statements on the current status of AMR in ICUs. This is an area that requires urgent attention.

What is clear from these limited data is that there is important geographical diversity when it comes to MDR and the mechanisms involved. This further challenges external validity of many of the epidemiological studies. This geographical diversity may not only be at the country level, but even within the same area or city, important variations may be present; hospital and unit specific data are required.

Gram-negative pathogens clearly are the major threat to patients in our ICUs today; it seems that the Gram-positive resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are more or less controlled and not perceived as an immediate threat by many clinicians. The most urgent challenges in the ICU are ESBL-producing Enterobacteraceae, CRE, MDR *Pseudomonas aeruginosa* and *Acinetobacter*. For many of these pathogens, the southeast of Europe seems to be a hotspot, but also elsewhere in Europe ESBL and CRE incidence is increasing. For CREs there seems to be considerable variability in enzyme distribution. Recently, colistin resistance has been identified as an emerging threat, which is particularly problematic as colistin is the backbone of many antibiotic schemes to treat MDR pathogens in severely ill patients (Marston et al. 2016).

Whereas in many countries these pathogens are found only in isolated cases or related to hospital-acquired infections and outbreaks, it is more worrying that they are becoming endemic in some countries. In the first case this poses few challenges for empirical therapy, but this is different when MDR pathogens spread in the community and may be involved in community-acquired infections as well. In these situations, more broad-spectrum antibiotics may be used, fuelling the problem of MDR and accelerating a vicious circle of increased antibiotic consumption, antibiotic resistance and increased length of stay.

Diagnostics and Risk Stratification – the Need for Speed

MDR infections pose specific problems not only to clinicians, but also to the microbiology lab. Classic microbiological techniques require multiple days until full AST can be reported and this is no longer acceptable with our current challenges. Rapid identification and susceptibility reporting are now the goal of many new techniques that are becoming available. New techniques such as matrix-assisted laser desorption/ionisation time-of-flight (MALDITOF) analysers, and polymerase chain reaction (PCR) based techniques drastically reduce time to reporting of problematic pathogens or particular resistance patterns (Mitsuma et al. 2013). While interesting in terms of performance, the true value of these systems should be assessed on the time to adequate therapy, overall antibiotic consumption and incidence of MDR infections in the unit as a whole. A strategy based on PCR to identify and isolate patients colonised with MDR pathogens could not reduce acquisition rates of multidrug-resistant bacteria in a large, international study (where hand hygiene compliance was high) (Derde et al. 2014).

This does not mean that trying to identify the patient at risk for infection with MDR pathogens should not be pursued. However, it is plausible that risk factors for MDR involvement are not uniform for all different MDR pathogens, which further complicates things. Common risk factors for MDR involvement include antibiotic exposure, previous stay in an acute or chronic care facility, the presence of comorbidities and chronic kidney disease requiring RRT (Martin-Loeches et al. 2015). The problem is that these factors are quite common these days, not only in hospital-acquired infections but also in community-acquired disease.

Antibiotic Therapy—Continued Efforts Necessary

As for all pathogens, antibiotic therapy remains the cornerstone of infection treatment. Empirical antibiotic therapy is especially challenging in endemic situations; this is where early risk stratification, probably combined with rapid diagnostic techniques, has its highest merits. This will allow selective targeting of patients at risk for infection with MDR pathogens while avoiding antibiotic overuse in the overall population. Whereas this may be more easy outside the ICU, we need to apply the same concept in critically ill patients.

Generally, combination therapy is recommended for MDR infections, particularly in the empirical phase but also for directed therapy for many pathogens.

Although resistance is increasing, many of our 'old antibiotics' are still of use in the treatment of MDR pathogens (Theuretzbacher et al. 2015). Based on our current knowledge though of antibiotic pharmacokinetics (PK) and pharmacodynamics (PD) in critically ill patients, dosing and antibiotic administration certainly are to be considered when treating MDR infections. Not only the dose itself is important—with doses generally higher compared to non-severe infections—but optimising PK/PD of antibiotics may also include the use of prolonged infusion e.g. for beta-lactam antibiotics. One critical limitation in this approach is the lack of detailed information about the susceptibility of the pathogen; the minimally inhibitory concentration (MIC) is important but not routinely available, and certainly not in the early phase of therapy using current technology. Additionally, for many drugs that are crucial for managing MDR infections, there are no solid PK and PD data available on which we can base solid dosing advice (colistin, fosfomycin, among others). To fully compensate for the changed PK in critically ill patients, therapeutic drug monitoring (TDM) may be a logical solution; this fits the trend towards personalised medicine, but up until now no study has demonstrated an advantage of TDM guided therapy in MDR infections.

New drugs are coming to the market that are specifically targeting MDR pathogens (Bassetti et al. 2015b). All of these are further developments in known antibiotic classes, and

there is a real risk of AMR developing against these newly developed drugs, particularly if these will be used on a large scale and in settings where basic concepts of infection prevention are lacking. It is our responsibility to use these antibiotics wisely, that is for the right indication (and pathogen), and for the correct duration.

Antibiotics that are of particular interest here are ceftolozane/tazobactam, avibactam combinations (ceftazidime, ceftaroline, aztreonam), plazomicin, new beta-lactamase-inhibitor plus carbapenem combinations and eravacycline. Until now most of these new drugs have been tested in complicated urinary tract infections and intra-abdominal infections only, but studies in infected critically ill patients are being performed and will inform us of their value in this precise setting.

Irrespective of the above, it is imperative to control antibiotic use in all patients through an integrated, multidisciplinary approach aimed at reducing antibiotic exposure and improving patient outcomes, commonly referred to as 'antimicrobial stewardship' (De Waele et al. 2016), which is discussed more extensively by Schouten on page 20.

Infection Control – a Crucial Cornerstone

Controlling transmission of MDR pathogens in the hospital is the main goal in infection control strategies, focusing mostly on hand hygiene, surveillance, patient isolation and environmental measures. Hand hygiene is one of the primary strategies of infection control measures, and indeed impacts transmission of high-risk pathogens such as MRSA or VRE (Derde et al. 2014). Equally important is environmental cleaning, which has long-time been ignored, particularly of beds and equipment that have had MDR-infected or -colonised patients in them.

Decontamination of the skin and GI tract, two important potential reservoirs of MDR pathogens, is more controversial. While selective digestive decontamination (SDD) and selective oral decontamination (SOD) have been proved to improve outcome in setting with low incidences of MDR, concerns about the effect of antibiotics used in SDD in high-MDR prevalence prevent wide adoption of this approach (Plantinga et al. 2015). Large-scale studies in these settings are currently underway. Skin decontamination with chlorhexidine (chlorhexidine bathing) remains controversial, and was found to reduce central line-associated bloodstream infections and MRSA infection, and to have the most effect when baseline infection rates are high (Frost et al. 2016).

One topic drawing much attention now is the impact of the microbiome on acquiring MDR pathogens. Faecal microbiota transplantation has been suggested as a possible strategy in the treatment of relapsing *Clostridium difficile* infections (Youngster et al. 2014) but may also be helpful to combat MDR colonisation. Many studies in this field are underway.

All of the above strategies however do not prevent transmission of mobile genetic elements encoding for AMR in the GI tract of our patients. Combined with widespread antibiotic use that greatly affects the microbiome and takes down our natural defence against colonisation with pathogens (Brooks and Brooks 2014), this exchange of resistance mechanisms in the gut is probably the biggest threat in Gram-negative MDR infections.

Conclusion

AMR has become a major concern in critical care medicine, and impacts the daily management of severe infections in many ICUs. Maximising appropriateness of antibiotic therapy in patients with infections due to MDR pathogens while minimising antibiotic exposure in all patients in the ICU and avoiding transmission of MDR pathogens are the main goals for which all healthcare workers in the ICU are responsible. Antibiotic therapy, while challenging, is still possible for most pathogens using both older antibiotics and the new drugs that will become available in the next years. An individualised approach incorporating PK/PD principles and also considering antibiotic susceptibility will further improve antibiotic effectiveness. Infection control measures remain important with hand hygiene as the key element; other interventions may be pathogen- or unit-specific. ■

Conflict of Interest

Jan De Waele declares Consultancy for AtoxBio, Bayer Healthcare, and Merck. He is Infection section Chair at the European Society of Intensive Care Medicine, President of the Belgian Society of Intensive Care Medicine, Past President of WSACS - the Abdominal Compartment Society and Senior Clinical Investigator at the Flanders Research Foundation.

Abbreviations

AMR antimicrobial resistance
AST antibiotic susceptibility testing
ESBL Extended-Spectrum beta- Lactamase
ICU intensive care unit
MDR multidrug resistance
MRSA methicillin-resistant Staphylococcus aureus
PCR polymerase chain reaction
PD pharmacodynamics
PK pharmacokinetics
PDR pan-drug resistance
TDM therapeutic drug monitoring
VRE vancomycin-resistant enterococci
XDS extensive drug resistance

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Antimicrobial Stewardship in the ICU

Treating patients with multidrug-resistant (MDR) pathogens is an increasing challenge for intensive care unit (ICU) physicians. In the ICU, compared to other hospital departments, severe infections are most prevalent and antimicrobial use is most abundant. Not surprisingly, antimicrobial resistance (AMR) has emerged primarily in the intensive care setting, where multiple facilitators for the development of resistance are present: high antibiotic pressure, loss of physiological barriers, and high transmission risk. There have been numerous reports on outbreaks with MDR pathogens in ICUs (French et al. 2017). In some parts of the world ICU physicians are struggling with the outlook of a "post-antibiotic era", where there are no antibiotics available to treat common ICU infections (MacVane 2017). With no new drugs in the pipeline for MDR pathogens, implementation of an antimicrobial stewardship programme (ASP) seems a reasonable pathway to help prevent the further development of resistance (Bassetti et al. 2016).

Definition

An ASP can be thought of as a menu of interventions that is adapted and customised to fit the infrastructure and organisation of an ICU (Septimus and Owens 2011). The most important goal of an ASP is to provide safe and effective antibiotic therapy whilst safeguarding its effectiveness for future generations. This can be accomplished by reducing the total consumption of antibiotics and ensuring their appropriate usage. Interventions to reach that goal in ICU include prescription of appropriate empirical therapy, optimal timing, optimal dosing, de-escalation and discontinuation (Schuts et al. 2016).

Most intensivists acknowledge the importance of antimicrobial stewardship, but have a hard time implementing an ASP in their own ICU. In this article, a stepwise approach to implementation is discussed (**Figure 1**).

How to Start?

First, one needs to take control of the basics. The ICU is—more than any department in the hospital—a place where medical specialists work closely together to provide the most optimal patient care. This is especially a challenge in the treatment of patients with infections, as infectious disease physicians, clinical microbiologists and clinical pharmacists, relying on their own expertise, all advise the ICU physician on the use of antibiotics. While the ICU has become an increasingly independent place and ICU physicians have engaged in expanding clinical expertise (e.g. ultrasound, continuous renal replacement therapy), in the field of treatment of AMR infections, cooperation with other clinical specialties remains crucial. It is pivotal that intensivists take part in discussions on the hospital antibiotic formulary and help develop local guidelines for the clinical disease entities that are frequently encountered in the ICU. Preferably, an intensivist is a member of the hospital antimicrobial management team. On a day-to-day basis, the presence of an attending infectious diseases physician, clinical microbiologist or clinical pharmacist on the ICU clinical ward round may add to mutual understanding and well-deliberated treatment decisions (Rimawi et al. 2013).

Data

Some essential baseline data is needed to define if antimicrobial use in your unit is appropriate. It is important to have regularly updated information on local resistance patterns from your microbiologist. It is also essential to be aware of what the prescribing patterns are in your unit. Expressed as days of therapy (DOT) or defined daily dose (DDD)/100 patient days, it is possible to get a general feel of the (differential) of antibiotic use in your unit over time and benchmark with other comparable ICUs. Apart from these quantitative metrics it may prove useful to measure current practice closer to the patient and prescribing physician level, e.g. by assessment of the percentage of appropriate empirical therapy according to the local guidelines or the percentage of patients with DOT according to local guidelines. One could use a simple PPS (Point Prevalence Survey) or perform a small prospective audit to evaluate most of these processes (Zarb et al. 2012). These figures all together will create a picture of the current state of antimicrobial treatment in your unit and point you to the problem most in need of improvement.

Barriers

Once the largest gap is recognised, insight must be gained into the factors that influence appropriate antimicrobial prescription at the ICU and an improvement strategy should be developed based on these factors while applying social and behavioural change theories. Antimicrobial prescription is a complex process that is influenced by many factors. The appropriateness of antimicrobial use in hospitals varies between physicians,

hospitals and countries, due to differences in professional background, clinical experience, knowledge, attitudes, hospital antibiotic policies, professionals' collaboration and communication, care coordination and teamwork, care logistics and differences in sociocultural and socioeconomic factors. This renders changing hospital antimicrobial use into a challenge of formidable complexity. Given that many influencing factors play a part, the measures or strategies undertaken to improve antimicrobial use need to be equally diverse.

Even in a single ICU setting, using relatively simple methods, these challenges can be met. A well-structured group discussion focused at barriers and facilitators that influence appropriate antibiotic use can lead to surprising insights.

Interventions

A recently published Cochrane review found that most interventions are effective in increasing compliance with antibiotic policies and reducing duration of treatment. Lower use of antibiotics does not increase mortality and likely reduces length of stay. Enabling (persuasive) strategies consistently improved the effect of interventions, including those with a restrictive component (Davey et al. 2017).

Most interventions to change antibiotic use that have been studied in ICUs are effective in reducing the quantity of antibiotic use and antibiotic related costs, but the effects on clinical outcome and—importantly—on resistance levels are less outspoken (Kaki et al. 2011). The most often studied strategy in ICU is to apply restrictive interventions, such as pre-authorisation of antibiotics, e.g. by an infectious diseases specialist, a restricted antibiotic list or an automated antibiotic stop order. These are generally very effective in the short term. However, restrictive measures may wear out prescribing physicians needing to ask for permission to prescribe. More importantly, it can induce a so-called "squeeze-the-balloon effect": by restricting one class of antibiotics, resistance will diminish for some microorganisms, but resistance to the alternative antibiotics that are used to replace the restricted ones will increase. In short, restrictive interventions are welcome in an acute outbreak setting, where there is a strong relationship between the particular antibiotic that is (over)used and the emerging resistant pathogen(s).

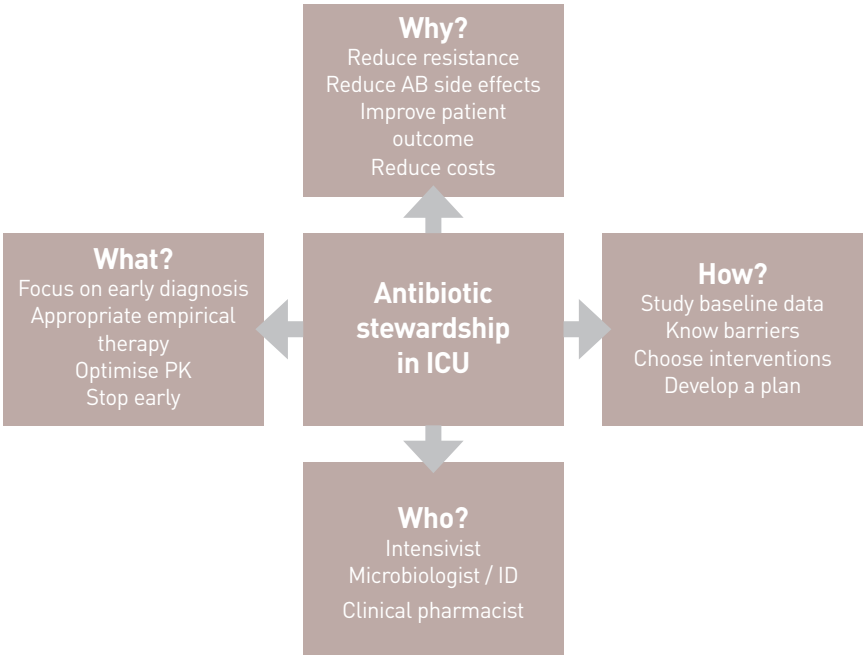

Figure 1. AB antibiotic ID infectious diseases PK pharmacokinetics

Table 1. Evidence-Based Recommendations to Increase the Appropriate Usage of Antibiotics in ICU Patients: a 5-Day Bundle

Source: De Angelis et al. (2012)

1st	the clinical rationale for antibiotic start should be documented in the medical chart at the start of therapy
	appropriate microbiological culture according to local and/or international guidelines should be collected
	the choice of empirical antibiotic therapy should be performed according to local guidelines
2nd	review of the diagnosis based on newly acquired microbiological cultures
	de-escalation therapy (the narrowest spectrum as possible) according to available microbiological results
3rd–5th	review of the diagnosis based on newly acquired microbiological cultures
	de-escalation therapy (the narrowest spectrum as possible) according to available microbiological results
	interruption of treatment should be considered according to local and/or international guidelines

Many non-restrictive "persuasive" interventions such as professional education, evidence-based clinical decision support systems and guidelines, audit and feedback and remind-

ers have also been shown to be successful in ICUs (Kaki et al. 2011; Mertz et al. 2015; Pestotnik et al. 1996).

There is a wide variety of interventions available, and the most difficult task is to choose the right one at the right time. These choices are preferably made based on the insights from a thorough barrier analysis as discussed above (Cabana et al. 1999; Flottorp et al. 2013): first comes diagnosis, then comes treatment! If a lack of awareness or knowledge in ICU professionals is the key problem, education could help. If, however, there is an attitude problem, an educational strategy may prove counterproductive, and academic detailing might work out better. Also, different aspects of appropriate antibiotic use (start, stop or change therapy) may require very different interventions (Schouten et al. 2005).

There is a growing body of evidence linking specific barriers to effective interventions. These can be selected and carried out. It is clear that there is no one-size-fits-all approach possible here. Rather, a more tailored approach is advocated, sometimes leading to multifaceted interventions comprising more than one type of intervention. Plan-do-study-act (PDSA) cycles can be used to target one relevant aspect of antibiotic care at the time, preferably going for the "low-hanging fruit" first.

Bedside Tools: Bundles and Biomarkers

In ICUs, bundle approaches have often been successful: e.g. surviving sepsis bundles, VAP bundles and CVC bundles have helped intensivists to apply the most important aspects of a specific care setting. There are some examples of antibiotic use bundles that cover the most relevant aspects of antibiotic use: start, streamline and stop (**Table 1**). Bundles are essentially reminders, and can be distributed as plastic flashcards, posters, a smartphone application or even integrated within the electronic medical record.

Biomarkers can also be used to reach antibiotic stewardship goals: the use of procalcitonin assays has been shown to influence ICU physicians to safely shorten duration of antibiotic therapy in ICU patients with an infection (Bouadma et al. 2010; de Jong et al. 2016).

Conclusions

In the absence of new antibiotics for difficult-to-treat infections by MDR pathogens, antibiotic stewardship is advocated in each ICU. ASPs aimed at combating antimicrobial resistance through improved antibiotic use will play an increasingly important role in the ICU. Implementation of an ASP requires a structured approach:

- First make sure the basics are taken care of: availability of information about resistance patterns and quantity and quality of antibiotic usage, engagement of a supportive team of antibiotic specialists and development of clear, locally adapted guidelines.
- Based on baseline figures, choose to target one problem at a time. Perform a thorough analysis to elucidate barriers to optimal antibiotic use using interviews or a focus group.
- Find the optimal strategy to overcome the barriers using the existing literature and common sense, involve quality of care/implementation experts to explore and implement.
- Repeat the same cycle with different targets and use PDSA to monitor progress. ■

Conflict of Interest

Jeroen Schouten declares that he has no conflict of interest.

Abbreviations

AMR antimicrobial resistance
ASP antimicrobial stewardship programme
DDD defined daily dose
DOT days of therapy
ICU intensive care unit
MDR multidrug resistance
PDSA plan-do-study-act

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Towards Safer Ventilation in Critically Ill Patients Without ARDS

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Invasive ventilatory support, one of the most frequently applied strategies in intensive care unit (ICU) patients, is increasingly recognised as a potentially dangerous intervention. Recognition of so–called ventilator–induced lung injury and the broad acceptance of lung–protective ventilation strategies in ICUs worldwide led to noticeable changes in ventilatory management (Putensen et al. 2009; Briel et al. 2010): low tidal volumes and higher levels of positive end–expiratory pressure (PEEP), respectively, to prevent overdistension and repeatedly opening and closing, are increasingly used in patients with acute respiratory distress syndrome (ARDS) (Checkley et al. 2008; Sutherasan et al. 2014; Esteban et al. 2013; Bellani et al. 2016). A high driving pressure level was recently documented as another potentially modifiable factor in ventilator–induced lung injury in one meta-analysis (Amato et al. 2015) and one large observational study (Bellani et al. 2016; Laffey et al. 2016) of ARDS patients. However, it remains uncertain what is the best way to lower the driving pressure level and also whether a strategy aiming at a lower driving pressure truly affects outcome.

While it is likely that these protective, or potentially protective strategies also benefit patients without ARDS (Serpa Neto et al. 2014a; 2015a; 2014b), changes in ventilatory support in these patients have been less impressive, and ventilator settings known to cause ventilator–induced lung injury in ARDS patients continue to be used in patients without ARDS (Azevedo et al. 2013; Lellouche et al. 2012). This is possibly due to the lack of robust and convincing randomised controlled trial (RCT) evidence for benefit of lung–protective ventilation strategies in patients without ARDS. We discuss the available evidence for benefit of protective ventilation strategies in patients without ARDS, including the use of low tidal volumes, higher levels of PEEP and lower driving pressure levels (**Table 1**).

Low Tidal Volumes

Evidence for benefit in patients without ARDS

Results of two RCTs suggest benefit from tidal volume reductions in critically ill patients without ARDS (Lee et al. 1990; Determann et al. 2010). One North American group of investigators studied the safety of tidal volume reduction from 12 to 6 ml/kg predicted body weight (PBW) in a cohort of ICU patients without ARDS (Lee et al. 1990). They found tidal volume reduction to be associated with a lower number of pulmonary complications and less time spent on the ventilator. A group of investigators in the Netherlands compared ventilation using tidal volumes of 10 ml/kg PBW with one using 6 ml/kg PBW (Determann et al. 2010). They found tidal volume reduction to be associated with less progression to ARDS. Time spent on the ventilator, however, was not different in this RCT.

Three meta-analyses including several observational studies as well as the two aforementioned RCTs (Serpa Neto et al. 2012; 2014a; 2015a) suggest tidal volume reduction to reduce time spent on the ventilator, duration of stay in the ICU and hospital, and also to prevent progression to ARDS.

Arguments against low tidal volumes in patients without ARDS

Several arguments against tidal volume reduction in patients without ARDS have been suggested. The compensatory higher respiratory rates needed with use of low tidal volumes could cause discomfort that potentially increases sedation needs (Ferguson 2012), risks of muscle weakness (Lipshutz and Gropper 2013), patient–ventilator asynchronies (Kallet et al. 2006; Kallet et al. 2001a) and atelectasis (Kallet et al. 2001b). Whether these assumed disadvantages of tidal volume reduction blunt the beneficial effects of prevention of overstretching of lung tissue seems unlikely, especially when considering that a tidal volume size of ~ 6 ml/kg PBW is seen as normal, and also most efficient in healthy mammals (Tenney & Remmers 1963). Certainly, critically ill invasively ventilated patients could never be seen as healthy individuals, but if one considers

these patients may develop atelectases we may even want to reduce tidal volume even below what we call normal.

Current Practice

Recent observational studies suggest that tidal volumes in patients without ARDS are often high, and at least higher than what is presumed safe for patients with ARDS (Linko et al. 2009; Chang et al. 2013; Elmer et al. 2013; Serpa Neto et al. 2016a). Interestingly, tidal volumes are also frequently higher than what ICU physicians say they prefer (Rose et al. 2014). Whereas the small decrease in tidal volumes over the last decade seems promising (Esteban et al. 2013; Serpa Neto et al. 2016a), still more than 30% of patients receive ventilatory support with tidal volumes >8 ml/kg PBW (Serpa Neto et al. 2016a).

PEEP in Patients Without ARDS

Evidence for Benefit

The results of four RCTs suggest benefit from higher levels of PEEP in critically ill patients without ARDS (Ma et al. 2014; Schmidt et al. 1976; Weigelt et al. 1979; Manzano et al. 2008). One Chinese group of investigators compared a strategy using PEEP between 11 and 30cm H_2O with one using PEEP between 3 and 10 cm H_2O (Ma et al. 2014). They found a higher level of PEEP to be associated with a larger number of patients that survived till day 28. Another team of investigators compared PEEP of 8 cm H_2O with PEEP of 0cm H_2O (Schmidt et al. 1976). They found a higher level of PEEP to be associated with less progression to ARDS. The same results came from a RCT by a North American group of investigators comparing PEEP of 5cm H_2O with PEEP of 0cm H_2O (Weigelt et al. 1979). Lastly, one Spanish RCT comparing PEEP of 5 to 8cm H_2O with PEEP of 0cm H_2O showed a lower incidence of ventilator–associated pneumonia in patients ventilated with higher levels of PEEP (Manzano et al. 2008).

One recently published meta-analysis that used data from all 21 investigations of PEEP in ICU patients without ARDS (Pepe et al. 1984; Nelson et al. 1987; Michalopoulos et al. 1998; Lago Borges et al. 2014; Carroll et al. 1988; Celebi et al. 2007; Borges et al. 2012; Borges et al. 2013; Holland et al. 2007; Dyhr et al. 2002; Marvel et al. 1986; Murphy et al. 1983; Zurick et al. 1982; Good et al. 1979; Vigil & Clevenger 1996; Cujec et al. 1993; Feeley et al. 1975), including the four positive RCTs mentioned above, however, suggests no benefit from using higher levels of PEEP regarding important clinical outcomes like mortality, duration of ventilation, and development of ARDS or pneumonia (Serpa Neto et al. 2016b). Of note, quality of the meta-analysed studies was at times low to very low, and there was substantial heterogeneity amongst the meta-analysed studies.

“Clear need for robust evidence from well–powered RCTs”

In the absence of high quality RCTs in ICU patients we may want to consider the results of RCTs comparing different levels of PEEP during intraoperative ventilation. The results of three well–performed RCTs suggest benefit from higher levels of PEEP in surgery patients without ARDS (Futier et al. 2013; Severgnini et al. 2013; Ge et al. 2013). Of note, these three RCTs all compared bundles of ventilation, i.e., a combination of low tidal volumes plus a higher level of PEEP vs. a combination of high tidal volumes plus lower levels of PEEP, which makes it difficult if not impossible to determine the individual effect of the higher levels of PEEP in these patients. A large RCT comparing high levels of PEEP with low levels of PEEP with similar tidal volumes during intraoperative ventilation, though, found no benefit of higher levels of PEEP regarding development of postoperative pulmonary complications (PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology et al. 2014). In addition a recent individual patient data meta-analysis using data from these four RCTs of intraoperative ventilation found a clear association between improved outcome and the intraoperative use of low tidal volumes, and not the use of higher levels of PEEP (Serpa Neto et al. 2015b).

Arguments Against Use of Higher Levels of PEEP

Two frequently mentioned arguments against the use of higher levels of PEEP in ICU patients without ARDS include the impact on the haemodynamic system (PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology et al. 2014), and the risk of overdistension (Serpa Neto et al. 2016c). Similar to other interventions, it could be that the beneficial effects of PEEP are not linear to its level, but rather U–shaped (Li et al. 2015; Gurudatt 2012; Bellamy 2006). The best level of PEEP then must be somewhere in between a (too) low and a (too) high level of PEEP. Indeed, a too low level of PEEP may fail to recruit sufficient amounts of collapsed lung tissue while increasing the afterload of the right ventricle of the heart. A too high level of PEEP may be able to recruit large amounts of collapsed lung tissue but also cause overdistension of nondependent lung tissue. Likely, the presence and severity of ARDS influences the shape of this hypothetical curve, which may at least in part explain why higher levels of PEEP have been found to be beneficial only in patients with moderate and severe ARDS, while not resulting in better outcomes in patients with mild ARDS (Briel et al. 2010) and patients without ARDS (Serpa Neto et al. 2016b).

Current Practice

A large worldwide observational international study showed that the average PEEP level used in patients without ARDS is low, with more than 50% of patients on PEEP ≤5cm H_2O (Serpa Neto et al. 2016a). In these patients the level of PEEP did not change much over recent years (Esteban et al. 2013; Serpa Neto et al. 2016a), although there are regional differences in use of PEEP. For instance, in the Netherlands, PEEP levels in patients without ARDS were found to be surprisingly higher compared to levels in neighbouring European countries in one large observational study (van IJzendoorn et al. 2014).

Driving Pressure in Patients Without ARDS

Evidence for Benefit

There is very little direct clinical evidence for beneficial effects of lower driving pressure

Table 1. Positive RCTs comparing different sizes of tidal volumes and different levels of PEEP, and running and planned RCTs comparing different sizes of tidal volumes and different levels of PEEP

Study	Year of publication	Country	Type of patients					Detailed results
Tidal volume				**Low tidal volume strategy**		**High tidal volume strategy**		
Lee et al.	1990	North America	Patients without ARDS	6 ml/kg PBW		12 ml/kg PBW		Lower incidence of pulmonary complications and less time spent on the ventilator in the low tidal volume arm
Determann et al.	2010	The Netherlands	Patients without ARDS	6 ml/kg PBW		10 ml/kg PBW		Less progression to ARDS in the low tidal volume arm
PReVENT trial (AMC-UvA)	Recruiting	The Netherlands	Patients without ARDS	4 to 6 ml/kg PBW		8 to 10 ml/kg PBW		Primary endpoint: ventilator–free days and alive at day 28
EPALI trial (Corporacion Parc Tauli)	Recruiting	Spain	Patients at risk of ARDS	≤ 6 ml/kg PBW		≥ 8 ml/kg PBW		Primary endpoint: progression to ARDS
PReVENT-IMIC trial (MORU)	Planned	Asian–Pacific countries	Patients without ARDS					Primary endpoint: ventilator–free days and alive at day 28
PEEP					**High PEEP strategy**		**Low PEEP strategy**	
Schmidt et al.	1976	North-America	Patients at risk of ARDS after surgery		8 cm H_2O		0 cm H_2O	Lower incidence of ARDS and other pulmonary complications in the high PEEP arm
Weigelt et al.	1979	North-America	Patients at risk of ARDS		5 cm H_2O		0 cm H_2O	Lower incidence of ARDS in the high PEEP arm
Manzano et al.	2008	Spain	Patients with a P/F > 250		5 to 8 cm H_2O		0 cm H_2O	Lower incidence of VAP and less hypoxaemia in the high PEEP arm
Ma et al.	2014	China	Patients with NPE		11 to 30 cm H_2O		3 to 10 cm H_2O	Lower 28-day mortality in the high PEEP arm
'RELAx' trial (AMC-UvA)	Planned	The Netherlands	Patients without ARDS		8 cm H_2O		Lowest level possible	Primary endpoint: ventilator-free days and alive at day 28

AMC-UvA Academisch Medisch Centrum – Universiteit van Amsterdam ARDS acute respiratory distress syndrome EPALI Preventive Strategies in Acute Respiratory Distress Syndrome MORU Mahidol Oxford Research Unit, Bangkok, Thailand NPE neurological pulmonary oedema P/F PaO_2 to FiO_2 ratio PBW predicted body weight PEEP positive end–expiratory pressure PReVENT Protective VENTilation in patients without ARDS PReVENT-IMIC PRotective VENTilation In Middle and low Income Countries RELAx Restricted versus Liberal positive end–expiratory pressure in patients without ARDS RCT randomised controlled trial VAP ventilator-associated pneumonia

levels, as there have been no RCTs that tested a ventilation strategy that aimed for lower driving pressure levels, neither in ARDS patients, nor in ICU patients without ARDS. One recent observational study in critically ill patients found lower driving pressures to be associated with lower mortality rates (Serpa Neto et al. 2016a).

In the absence of RCTs in ICU patients we may want to consider the results of a recently published individual patient data meta-analysis including RCTs comparing different ventilation strategies during intraoperative ventilation (Serpa Neto et al. 2016). This meta-analysis suggests, firstly, that the driving pressure level per se seems to be associated with occurrence of postoperative pulmonary complications, and secondly that changes in the level of PEEP that resulted in a rise of the driving pressure level are associated with an increased occurrence of postoperative pulmonary complications. One plausible explanation could be that the rise of the driving pressure level is caused by overdistension induced by higher levels of PEEP, which may result in postoperative pulmonary complications, but this hypothesis remains to be tested in RCTs.

Arguments Against Low Driving Pressures

All studies performed so far comprise subanalyses of protective ventilation strategies using a certain level of PEEP with low tidal volumes. The balance between disadvantages and advantages of strategies specifically aiming at lower driving pressure levels remains uncertain. It is even more uncertain if a strategy aiming at a lower driving pressure is feasible, i.e., really reduces the driving pressure level below a certain level at which we consider the driving pressure level to be safe. Actually, we do not have a clue what we can call a safe driving pressure level. One additional problem is that patients without ARDS are more often receiving supported modes rather than mandatory modes of ventilation. This is where we encounter another hurdle: how to measure the driving pressure adequately in those patients?

Current Practice

A recently published large worldwide observational study shows the driving pressure level in patients without ARDS to vary between 9 and 13cm H_2O (Serpa Neto et al. 2016a). Other studies are highly needed to confirm this finding, and of course RCTs that test whether a ventilation strategy aiming for lower driving pressure levels really improves outcome of patients without ARDS.

Future Directions

There is a clear need for robust evidence from well–powered RCTs for use of low tidal volumes, PEEP and strategies that aim at low driving pressure levels in critically ill patients without ARDS. At present, two European multicentre RCTs, the Protective Ventilation in Patients without ARDS at Start of Ventilation (PReVENT) trial (AMC-UvA n.d.), and the Preventive Strategies in Acute Respiratory Distress Syndrome (EPALI) trial (Corporacion Parc Tauli n.d.) are investigating the impact of tidal volume reduction on outcome of ICU patients without ARDS. PReVENT is a Dutch multicentre RCT comparing low tidal volumes (4 to 6ml/kg PBW) with conventional tidal volumes (8 to 10ml/kg PBW) but a maximum plateau pressure of 25 cm H_2O (AMC-UvA n.d.). EPALI is a Spanish multicentre RCT comparing low tidal volumes (≤6ml/kg PBW) to conventional tidal volumes (8ml/kg PBW) in patients at risk for ARDS (Corporacion Parc Tauli n.d.). The primary endpoints of PReVENT and EPALI are the number of ventilator–free days and alive at day 28, and development of ARDS respectively. We ourselves have also initiated a multicentre RCT comparing low to high tidal volumes in Asian countries, the Protective Ventilation in Patients without ARDS at Start of Ventilation in Middle Income Countries (PReVENT-IMIC) (MORU, n.d.), using the same endpoint as in PReVENT. The REstricted versus Liberal positive end–expiratory pressure in patients without ARDS (RELAx) trial, a multicentre RCT comparing a standard level of PEEP of 8cm H_2O with the lowest possible level of PEEP in ICU patients without ARDS, is planned to start in the Netherlands in 2017. To the best of our knowledge no other RCTs that compare ventilation strategies aiming at different driving pressure levels in ICU patients without ARDS are presently planned. ■

Conflicts of interest

Fabienne Simonis declares that she has no conflict of interest. Marcus J. Schultz declares that he has no conflict of interest. Antonio Artigas Raventós declares that he has no conflict of interest.

Abbreviations

AMC-UvA Academisch Medisch Centrum
ARDS acute respiratory distress syndrome
MORU Mahidol Oxford Research Unit, Bangkok, Thailand
PBW predicted body weight
PEEP positive end-expiratory pressure
RCT randomised controlled trial

For full references, please email editorial@icu management.org or visit https://iii.hm/8xd

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Quantitative EEG in ICU

Useful and Feasible

EEG measures continuously at the bedside the human brain's electrical activity. Its main advantages are noninvasiveness, good spatial and temporal resolution, and sensitivity to changes in both brain structure and function.

In ICU, seizures are frequent in patients with/without acute brain injury. They are often difficult to recognise, because they are non-convulsive. This provides support in favour of continuous EEG (cEEG) rather than "spot" EEG, typically for a period of less than 30 minutes. cEEG refers to the recording of EEG over extended time periods in critically ill patients at risk for secondary brain injury and neurologic deterioration. Unfortunately, intensivists aren't usually trained in interpreting EEG, due to difficulties in interpretation of the recordings. Usually a neurophysiologist's consult is required. For this reason, EEG has been usually recorded on the spot, and it has not been deemed a potentially useful tool for continuous monitoring of the damaged brain, except in some neurological institutions. Fortunately, times are changing.

Indications for Continuous EEG Recording in ICU

Several guidelines recommend the use of cEEG in the ICU setting (Claassen et al. 2013; Le Roux et al. 2014; Claassen and Vespa 2014; Herman et al. 2015) for:

1. The diagnosis of nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE). NCSE is a state of continuous/repetitive seizures without convulsions. Due to the nonspecific signs and significant morbidity and mortality associated with NCSE, research has focused on early diagnosis and seizure termination. Standard EEG misses identifying NCSE in more than 75% of cases. Instead cEEG (lasting 6-12 hours or longer) is able to identify up to 80% of NCSE (Friedman et al. 2009). NCS are associated with such secondary insults as increased intracranial pressure, reduction in tissue oxygenation, and local metabolic derangements. Therefore, even if the effect of NCS identification and management on outcome has not been fully proven, untreated NCS is associated with increased mortality and increased risk for poor neurologic outcome. Therefore early identification of NCS with cEEG in patients with unexplained altered level of consciousness is strongly recommended (Sutter et al. 2016).

2. The assessment of efficacy of therapy for seizures and status epilepticus, when sedation and high-dose suppressive therapy, after first-line therapies, are required.

3. The identification of cerebral ischaemia. cEEG could detect delayed cerebral infarction in subarachnoid haemorrhage patients before clinical deterioration and CT scan changes become evident. In fact, the reduction of the ratio between alpha (8-13 Hz) and delta (<4 Hz) frequency, with an increase in slow frequencies, is becoming an interesting application of cEEG (Claassen et al. 2004; Rots et al. 2016).

4. The expansion of multimodality monitoring (MMM) of the injured brain, adding continuous information on the function of the cerebral cortex and its metabolic and functional variations. Advanced MMM should integrate neurophysiological information with neuroimaging and different continuous physiologic data, such as ICP, CPP, and $PbtO_2$, with EEG-derived parameters (Citerio et al. 2015).

Barriers and Possible Solutions for Implementing cEEG in ICU

Even if the indications are rather clear, ICU practice is far from a diffuse implementation of cEEG. Barriers to its implementation are here summarised, along with possible solutions for overcoming these obstacles:

• Limited availability of EEG technicians and neurophysiologists to review the studies 24/7.

In the UK, for example, a survey documented that only a minority of ICU units (33%) have access to continuous EEG monitoring, despite it being considered fundamental for patients' management (Patel et al. 2015). In a larger USA survey, continuous EEG is more frequently utilised (Gavvala et al. 2014). However, a substantial interhospital variability has been described. In a single centre study, only a minority (27%) of critically ill patients presenting criteria for EEG monitoring had an EEG recording (Park and Boyd 2015).

A possible solution is the integration of ICU staff in the continuous evaluation of the EEG recording. In our unit, after a standard EEG, EEG technicians position the electrodes with ICU nurses' help. Nurses have been trained to check the recording hourly and to reposition the electrodes if not working and to use a transparent dressing for stabilising the electrodes over time. Daily check of the system is planned by neurophysiologist technicians. Neurophysiologists discuss with ICU doctors the indications for monitoring and, on a daily basis, discuss the 24-hour recordings with ICU staff. ICU doctors and residents, present 24/7, have been trained to identify the most significant patterns utilising derived parameters as quantitative EEG (see below).

• Lack of uniform terminology and of consensus on the clinical significance of selected EEG patterns.

Neurophysiologists defined some criteria (Leitinger et al. 2015) for NCS identification, but variability in EEG interpretation still remains (Rodriguez Ruiz et al. 2016). Intensivists using cEEG need to focus on important items, i.e. outcome-related patterns. In our experience, we targeted to identify during the cEEG monitoring phase:

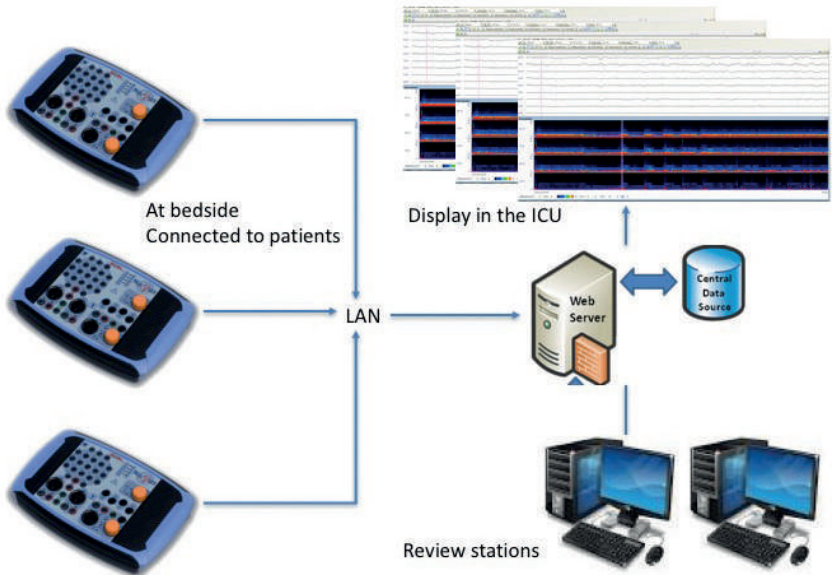

Figure 1.

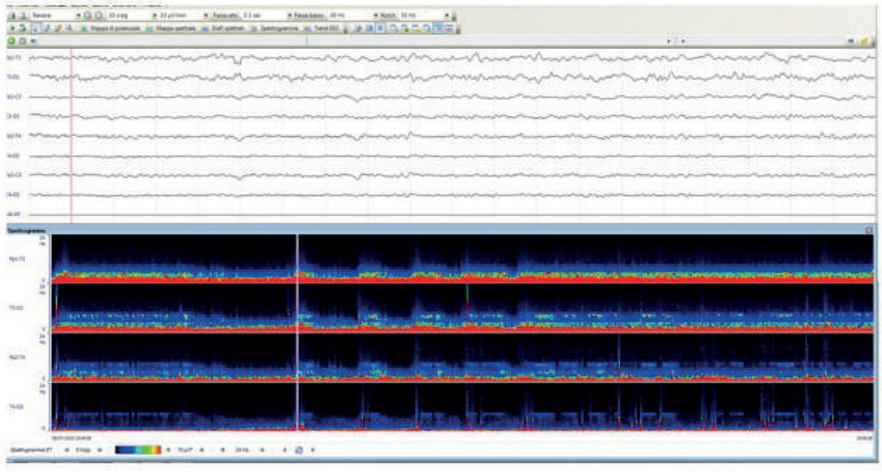

Figure 2.

- Artefacts
- Seizures
- Sedation level
- Asymmetry

• Need for an infrastructure for cEEG in a busy modern ICU environment.

Ideal tools are cheap, small, capable of being fully networked, with the possibility to review the recording in several locations. **Figure 1** presents the setting actually used in the San Gerardo Neurointensive Care Unit. Several small EEG patients' units are networked. In the ICU, the recordings are displayed at nursing and medical stations. Review stations, two in the ICU offices and the third in the neurophysiologists' offices, are available. All the data are stored on a dedicated server.

• Huge amount of recorded EEG-data requires time for reviewing and interpretation. Quantitative EEG (qEEG), could reduce the time required for reviewing hours of recordings (Haider et al. 2016). However, it is imperative to summarise and simplify. qEEG, defined by the American Academy of Neurology (Nuwer 1997) as "*the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison*", could help intensivists in reaching this aim. The huge amount of data is "digested" by a computer and summarised in a more accessible format. After a learning period, typical patterns, such as seizures, could be easily identified by non experts.

If we want to utilise cEEG as a monitoring tool, continuous evaluation of these recordings is needed. Moreover, for making the monitoring useful in the patient's care plan, intensivists, while detecting a pathological condition (i.e. seizures or oversedation), have to react, modifying their therapeutic approach.

> **"Intensivists using cEEG need to focus on outcome-related patterns"**

Implementation of qEEG: Summary of Our Experience

We studied the implementation of qEEG in our Unit in the clinical trial *Continuous Quantified EEG in NeuroIntensive Care (CrazyEEG)*, NCT02901262 (clinicaltrials.gov/ct2/show/NCT02901262), following these steps:

Phase 1. Definition of a cEEG recording setting.

The neurophysiologists and the intensivists defined a common setting for the study. Continuous EEG was recorded using 8 electrodes arranged according to the 10-20 International System, on a bipolar longitudinal montage plus a ground and a reference electrode.

Our c/qEEG setting includes:

- Continuous raw EEG tracings, useful for the neurophysiologist check of the Density Spectral Array (DSA) data,
- DSA is an EEG power-based display used to convey the frequency and power distribution of the EEG signal over time.
- Amplitude-integrated EEG (aEEG). Amplitude-integrated EEG expresses the amplitude compressed on a logarithmic scale of the EEG with an upper margin and a lower margin showing the highest and the lowest amplitude of EEG in a time period. It represents the collective electrical energy of neuronal firing.
- Burst suppression rate (BSR), measuring the amount of time within an interval spent in the suppressed state. This ratio increases as the brain becomes progressively less active, and it is an indicator of pharmacological suppression intensity.

Figure 2 depicts a raw EEG (30 sec) and

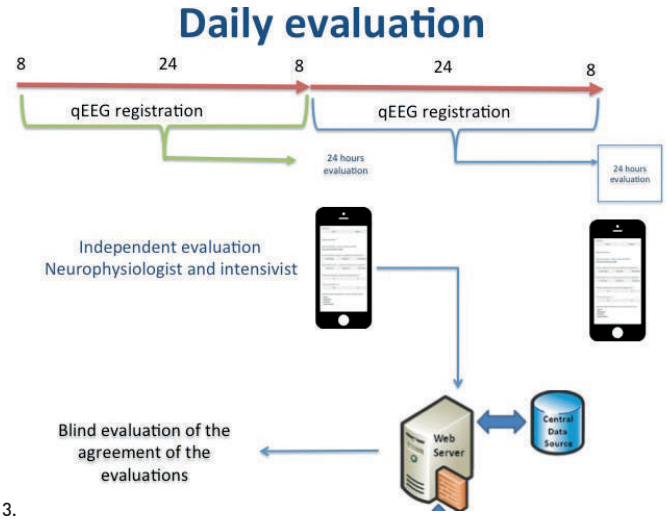

Figure 3.

the qEEG of the last 24 hours of recordings in the same patient. In the bottom part of the figure, the Density Spectral Array (DSA) is obtained from raw data using a Fourier transformation that gives the power contained within the various frequency bands, and is represented on a x-y graph that shows the time on the x axis and colours corresponding to the power at different frequencies on the y axis.

cEEG was recorded accordingly to the previously presented guidelines, including unexplained neurological status based on clinical history and imaging, frequent seizures and status epilepticus suspicion and management.

Phase 2. Baseline evaluation and neurophysiology training.

Intensivists were exposed to online training using the Clinical Electroencephalography for Anesthesiologists presentation developed by Purdon and Brown at Massachusetts General Hospital (**https://iii.hm/7x4**).

We anonymously tested the baseline knowledge on qEEG after the online course using a web-based system. Ten recordings with the display defined in step 1 were randomly presented. We evaluated the ability to:

1. assess the depth of sedation
2. evaluate symmetry between the hemispheres
3. recognise seizures and
4. recognise artefacts

The responses from intensivists were compared to those of two experienced neurophysiologists, used as "gold standard". We were disheartened after this step. Intensivists were not so good in interpreting qEEG.

After the baseline test, the intensivists received formal neurophysiology training consisting of lectures and discussion with the neurophysiologist of the recorded qEEG, integrating qEEG data with the clinical status and management strategies of the patients.

Phase 3. Check of the interpretation of qEEG after a 6-month learning period.

We compared qEEG evaluation by intensivists with the neurophysiologists' interpretation after 6 months of exposition and daily discussion. An app was developed for this aim (**Figure 3**). Every 12-24 recording period has been evaluated by the intensivist and by the neurophysiogist independently and blindly. We compared the responses after the first 25 patients.

The depth of sedation was correctly evaluated by intensivists in 90.7% of cases, artefacts in 95.3% of cases, symmetry in 81.4% of cases and seizures in 80.2% of cases.

Conclusions

The implementation of a qEEG system, supported by frequent interaction with a neurophysiologist, boosted the use of cEEG in our ICU.

ICU physicians cannot fully substitute for a neurophysiologist. Nevertheless, if they focus on clinically relevant questions (i.e. presence of seizures) they can gain sufficient knowledge to identify potentially dangerous conditions and for starting timely treatment. ■

Conflict of Interest

Giuseppe Citerio declares that he has no conflict of interest.

Abbreviations

aEEG amplitude-integrated EEG
cEEG continuous EEG
BSR Burst suppression rate
c/qEEG continuous quantitative EEG
CPP cerebral perfusion pressure
DSA Density Spectral Array
EEG electroencephalogram
ICP intracranial pressure
MMM multimodality monitoring
NCS nonconvulsive seizures
NCSE nonconvulsive status epilepticus
$PbtO_2$ partial pressure of brain tissue oxygen
qEEG quantitative EEG

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Utility of Brain Ultrasound in Neurocritical Care

Evidence shows that sonography of the brain can be used to visualise most of the intracranial structures, allowing estimation of the risk posed by life-threatening conditions, such as raised ICP, intracranial haematoma, hydrocephalus and midline shift.

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Brain ultrasound is increasingly used in the critical care setting. This technology is noninvasive, associated with low radiation exposure, and available at the bedside. Thanks to recent technological advances, sonography of the brain can be used to visualise most of the intracranial structures (Bogdahn et al. 1990). In complement to transcranial Doppler, brain ultrasound can be performed to estimate the risk of raised intracranial pressure (ICP), using ocular sonography of the optic nerve sheath, as well as monitor intracranial haematoma or hydrocephalus, and precisely measure midline shift.

Optic Nerve Sheath Diameter Measurement Using Ocular Sonography

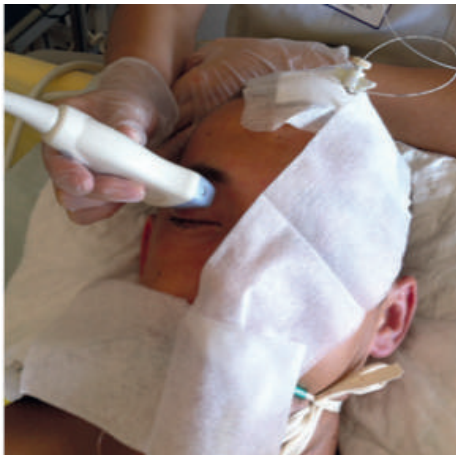
In 1806 Tenon described the optic nerve sheath and the optic sclera as continuous with the dura mater. In vivo, the cerebrospinal fluid (CSF) circulates in this space, from the posterior to the anterior part. This CSF is subject to similar pressure changes to those in the intracranial and lumbar compartments (Liu and Kahn 1993; Hansen and Helmke 1996). The retrobulbar part of the perioptic subarachnoid space is surrounded by fat and is therefore distensible. The optic nerve sheath diameter (ONSD) can increase as pressure raises and is accessible to ultrasonographic measurement. In 1997 Hansen and Helmke showed for the first time in humans that after an intrathecal lumbar infusion of Ringer's solution ONSD dilation reaches a maximum at peak CSF pressure (Hansen and Helmke 1997). This close relationship between ICP and dilation of the orbital perineural subarachnoid space has been confirmed by other studies using ultrasound (Blaivas et al. 2003; Geeraerts et al. 2007) and magnetic resonance imaging (Geeraerts et al. 2008; Rohr et al. 2011; Kimberly and Noble 2008). In 2011 two meta-analyses concluded that there is an excellent correlation between invasive ICP and ONSD (Dubourg et al. 2011; Moretti and Pizzi 2011). The exact cut-off of ONSD that may predict an ICP above 20mmHg remains to be determined. All the studies but one found that a cut-off between 5.2 and 5.9mm predicted an ICP above 20mmHg (Rajajee et al. 2011). Using the 5.9mm threshold, the sensitivity was 95% and the specificity 79% (Dubourg et al. 2011).

A high frequency, superficial probe of at least 7.5MHz must be used. Depth should be set at 4cm, and the two-dimensional mode used. The ONSD should be measured 3mm behind the retina in the nerve axis (**Figure 1**). A thick layer of gel is applied over the closed upper eyelid and the probe is placed on the lateral area of the closed eye. It has been shown that ONSD measured in the transversal plane is consistently larger than the one in the sagittal plane (Blehar et al. 2008).

We suggest that ONSD should be used as a triage tool to assess patients who are at risk for raised ICP and who should be referred to a neurocritical care unit, or to assess patients when there is no possibility to continuously monitor ICP.

Intracranial Imaging

In 1993 Becker et al. described the performance of transcranial duplex sonography (TDS) to distinguish ischaemic stroke and intracranial haematoma in 48 patients (Becker et al. 1993). Haematomas are hyperechogenic and brain ischaemia is hypoechogenic. Of the 28 patients with intracranial haematoma, the CT findings were confirmed in 24 using sonography. The main cause for failure was a poor acoustic window. Intraventricular haemorrhage was correctly found in all patients with a good acoustic window. Maurer et al. (1998) compared TDS and CT scan usage to diagnose stroke aetiology in 151 patients admitted for acute neurologic deficit in a simple blinded prospective study. A poor acoustic window was observed in 18 patients. Correct sonographic diagnosis of intracranial haematoma (in comparison to CT scan findings) was made in 126 patients, with a sensitivity and specificity of 94% and 95% respectively. The evaluation of the volume of the haematoma in the acute phase (< 3 hours from onset), when TDS evaluation was possible with a correct acoustic window, has been described to be feasible with good reproducibility (Perez et al. 2009). However, the volume of ischaemic brain injury is not accurately measured using sonography.



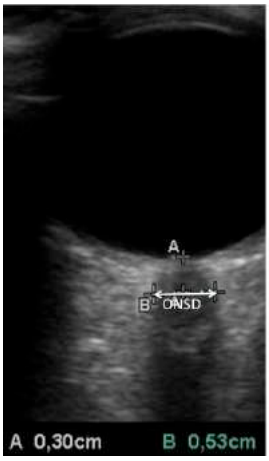


Figure 1. Ocular Sonography with Optic Nerve Sheath Diameter Measurement

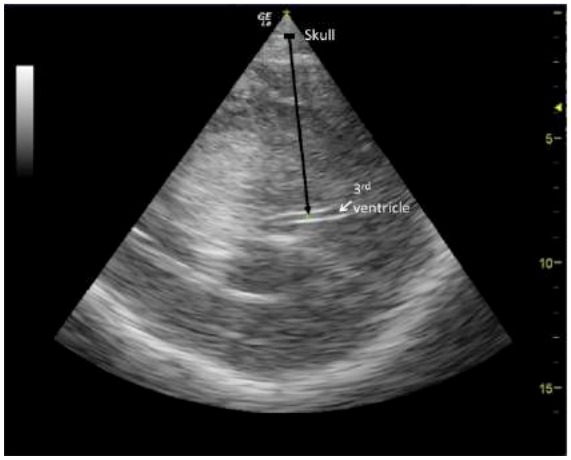


Figure 2. Brain Sonography for Midline Shift Assessment by Measuring the Distance Between the Skull and the Third Ventricle. This measure must be done at both sides to estimate the midline shift (difference/2).

An excellent correlation between the application of TDS and CT scanning for the measurement of the size of the third ventricle (r=0.95) and the frontal horn of the lateral ventricle (r=0.92) has been described (Becker G et al. 1994). In this study, TDS was applied to patients with known hydrocephalus from several causes, including subarachnoid haemorrhage, normal pressure hydrocephalus and brain tumours, with the third ventricle larger than 9mm and the frontal horn of the lateral ventricle larger than 19mm on the CT scan. The accurate sonographic measurement of ventricle size has been confirmed by several studies (Seidel et al. 1995; Kiphuth et al. 2011). External ventricular drainage placement has also been shown to be possible using sonography.

Brain Midline Shift

Brain midline shift (MLS) is a life-threatening condition that requires urgent diagnosis and treatment (Becker et al. 1977; Vollmer 1991). Seidel et al. described in 1996 a simple method to determine MLS with sonography by measuring the distance between the skull and the third ventricle at both sides in ischaemic stroke patients (**Figure 2**) (Seidel et al. 1996). Ultrasound MLS correlates well with findings on CT (Stolz et al. 1999; Bertram et al. 2000; Tang et al. 2006; Horstmann et al. 2009), and is an early predictor of outcome in acute stroke patients (Gerriets et al. 1999; 2001). Recently, a good agreement between the use of CT and sonography for MLS assessment in neurocritical care patients was confirmed (Motuel et al. 2014).

Conclusion

Brain ultrasound is a promising tool for the management of neurocritical patients, enabling the risk of life-threatening conditions to be estimated. As discussed, these include raised ICP, intracranial haematoma, hydrocephalus and midline shift. The main limitation is the relatively important percentage of patients with a poor acoustic window (5-10%). Use of brain ultrasound in the very early management of neurocritical care patients might enable physicians to better estimate the risk for acute neurosurgical emergencies that require urgent treatment such as osmotherapy. ■

Conflict of Interest

Timothée Abaziou declares that he has no conflict of interest. Thomas Geeraerts declares that he has no conflict of interest.

Abbreviations

CSF cerebrospinal fluid
MLS mid-line shift
ONSD optic nerve sheath diameter
TDS transcranial duplex sonography

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Albumin Administration in Sepsis

The Case For and Against

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Serum albumin is an essential plasma protein, with a variety of homeostatic and predictive roles in health and disease (**Figure 1**). Hypoalbuminaemia is common in critical illness. Human albumin solution has been administered clinically for more than five decades, but its use has been subject to marked controversy for the last twenty years (Fanali et al. 2012). This has shaped not just day-to-day practice in the intensive care unit (ICU), but also the evolution of international, multicentre randomised controlled trials (RCTs) in critical care. The most recent data from the United States suggests that, at least in academic medical centres, albumin administration is increasing, particularly among surgical patients and those with higher illness severity scores (Suarez et al. 2017). In Australia and New Zealand, although overall artificial colloid use has recently fallen, sales of 4% and 20% albumin solutions have remained constant (Glassford et al. 2016; Hasmmon et al. 2015). However, significant regional and international variation in the acceptability of albumin for use as a resuscitation fluid has been demonstrated (Finfer et al. 2010; McIntyre et al. 2016; Glassford et al. 2016). Some centres have even instituted intervention programmes to reduce albumin administration (Lyu et al. 2016), as the financial implications of albumin use can be considerable. In Australia, for example, regulations regarding blood product processing and distribution facilitate the administration of albumin by clinicians. In other countries, such as the UK, they can make it prohibitively expensive.

Controversial Fluid or Controversial Analysis?

In 1998 a systematic review written by the Cochrane Injuries Group and published in the *BMJ* attempted to synthesise the extant literature on albumin administration in the critically ill (Cochrane Injuries Group Albumin Reviewers 1998). In 24 highly heterogeneous studies reporting mortality, in which a total of 1204 patients were randomised to receive albumin (or plasma protein fraction) or an alternative (no albumin or a crystalloid solution), albumin was shown to be associated with a significant increase in mortality (OR 1.68, 95% CI 1.26 to 2.23). In 14 of these studies, the patient population was surgical, in 9 the patients were included once diagnosed with hypoproteinaemia or hypoalbuminaemia, in 4 following trauma, and in 3 following burns. Sepsis was only definitively mentioned as a feature of the population of a single trial. On sub-group analysis, when albumin was given to mainly surgical or trauma patients for the correction of hypovolaemia, there was no statistically significant increase in mortality (OR 1.46, 95% CI 0.97 to 2.22). Moreover, on exclusion of the 11 trials at greatest risk of bias, the odds ratio for mortality following albumin administration to correct hypovolaemia fell (OR 1.39, 95% CI 0.8 to 2.4). The included trials were small, clinically heterogeneous, prone to bias, and many had been performed 10 to 20 years previously. The meta-analysis excluded those studies where patients were randomised but no deaths occurred. In addition, albumin was compared to a variety of different, or unrecorded fluid types. While acknowledging the limitations of their findings, the authors called for a review into the routine use of albumin and for a rigorous randomised, controlled examination of its efficacy (Cochrane Injuries Group Albumin Reviewers 1998).

This publication was met with a flurry of rapid responses and editorials (Workman 1999; Dearlove 1999; Offringa 1998a; Berger 1998; Offringa 1998b; Shwe and Bhavnani 1998; Chalmers 1998; Frame and Moiemem 1998; Goodman 1998; Beale et al. 1998; Soni 1998; Riordan et al. 1998; Nadal et al. 1998; Petros et al. 1998; Nel 1998; McClelland 1998; Lawler and Morgan 1998; Fogarty and Khan 1999; Kaag and Zoetmulder 1998), including harsh criticism of the study, and statements of support opposing further albumin use (Offringa 1998a), which were almost immediately "clarified" (Offringa 1998b). Mainstream media presented a picture of significant harm (BBC News 1998; Murray 1998; Mills 1998). One letter to the *BMJ* from an academic at the UK Cochrane Centre in Oxford, who claimed he would "sue anyone who gave me an albumin infusion" (Chalmers 1998), led to further incendiary media coverage (Boseley 2000). This debate may also have contributed to the subsequent widespread adoption of transparent declarations of conflicts of interest in any submissions to peer-reviewed journals, including letters and rapid responses (Dearlove 1998; Chalmers 1998; Smith 1998).

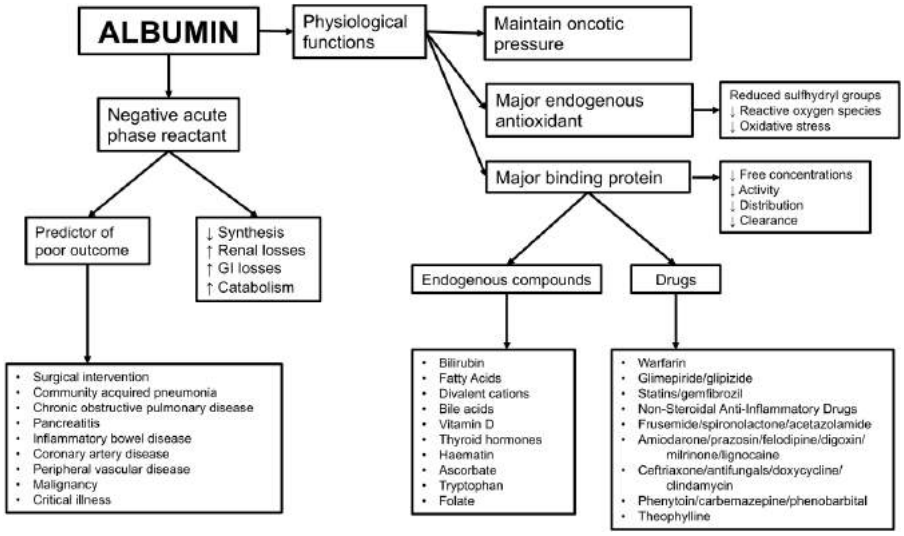

Figure 1. Physiological Functions of Albumin in Health and Disease

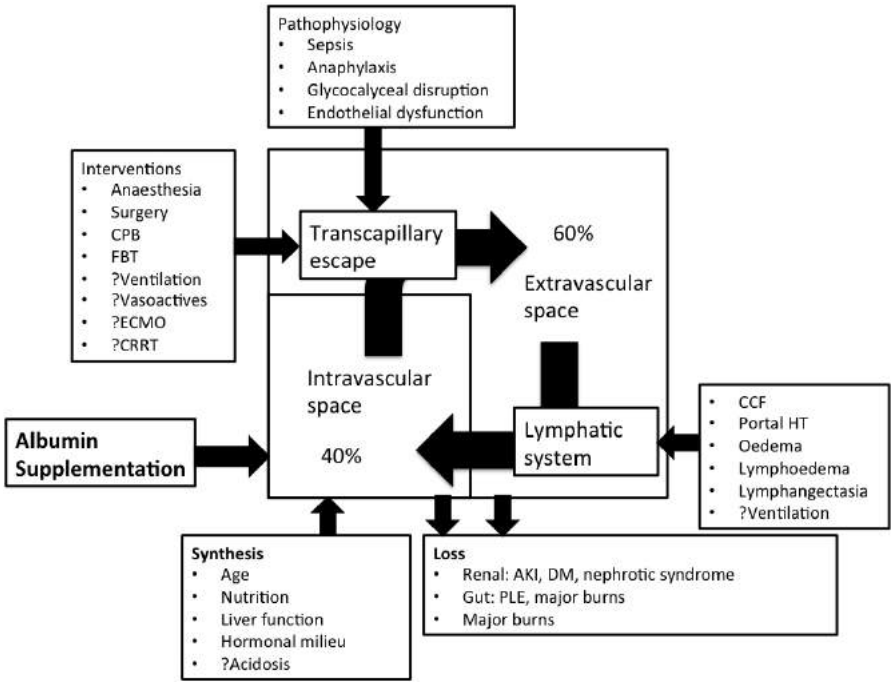

Figure 2. Albumin Homeostasis and Albumin Supplementation

CPB cardiopulmonary bypass BFT fluid bolus therapy ECMO extracorporeal membrane oxygenation CRRT continuous renal replacement therapy CCF congestive cardiac failure HT hypertension AKI acute kidney injury DM diabetes mellitus PLE protein-losing enteropathy

An international attempt to document the annual use of colloids in industrialised countries showed a significant reduction in the use of albumin between 1995 and 2006, with a concomitant increase in the use of synthetic colloids over the same period. However, the data was difficult to obtain, from fragmentary sources, and in many cases incomplete (Jones et al. 2010). An industry-sponsored report suggests a non-statistically significant 19% reduction in the volume of albumin supplied between 1998 and 2000, with an average of 5.4 million litre-equivalents of 4% albumin being sold each year (Vincent et al. 2003). Although it is impossible to assign causation, a survey of British ICU directors indicated that the use of albumin in more than half of UK ICUs had been influenced by this systematic review (Brown et al. 2001)

Establishing a SAFE Starting Point

As a response to the continued uncertainty regarding the use of albumin, in 2004 the Australia and New Zealand Intensive Care Clinical Trials Group published the *Saline versus Albumin Fluid Evaluation* (SAFE) Study.

SAFE was the first high-level, randomised, double-blind controlled evidence in 6,997 patients from 16 ICUs that 4% albumin administration was, well, safe. No differences were reported in 28-day all-cause mortality, need for mechanical ventilation or renal replacement therapy, and length of hospital or ICU stay between those critically ill patients requiring intravascular volume expansion given saline and those given albumin (Finfer et al. 2004). However, the SAFE trial was neither designed nor powered to demonstrate superiority to saline in different groups of critically ill patients—merely that its use was safe in the heterogeneous population of the ICU. Thus, albumin may be the fluid of choice in certain groups of patients, or under certain circumstances contra-indicated. A non-statistically significantly increased risk of mortality with albumin administration in trauma patients, and a similarly non-statistically significant reduction in mortality in patients with sepsis were observed in the trial, and further analyses of these subgroups were made (Myburgh et al. 2007; Finfer et al. 2011).

Is Albumin SAFE in Sepsis?

In septic patients, human albumin solution can be given for two broad indications—to restore or protect or expand intravascular volume, or to supplement serum albumin in an attempt to ameliorate the perceived deleterious effects of hypoalbuminaemia often associated with sepsis and/or critical illness. Although physiological reasoning suggests that albumin supplementation in the critically ill would be biologically logical, and the benefits of albumin use for fluid bolus therapy may be thought to be greatest among hypoalbuminaemic patients, the interaction between endogenous albumin concentrations and exogenous supplementation appears to be more complex (**Figure 2**).

In the 1,218 SAFE patients with sepsis there were no significant demographic differences between the saline and albumin groups at baseline. However, patients receiving

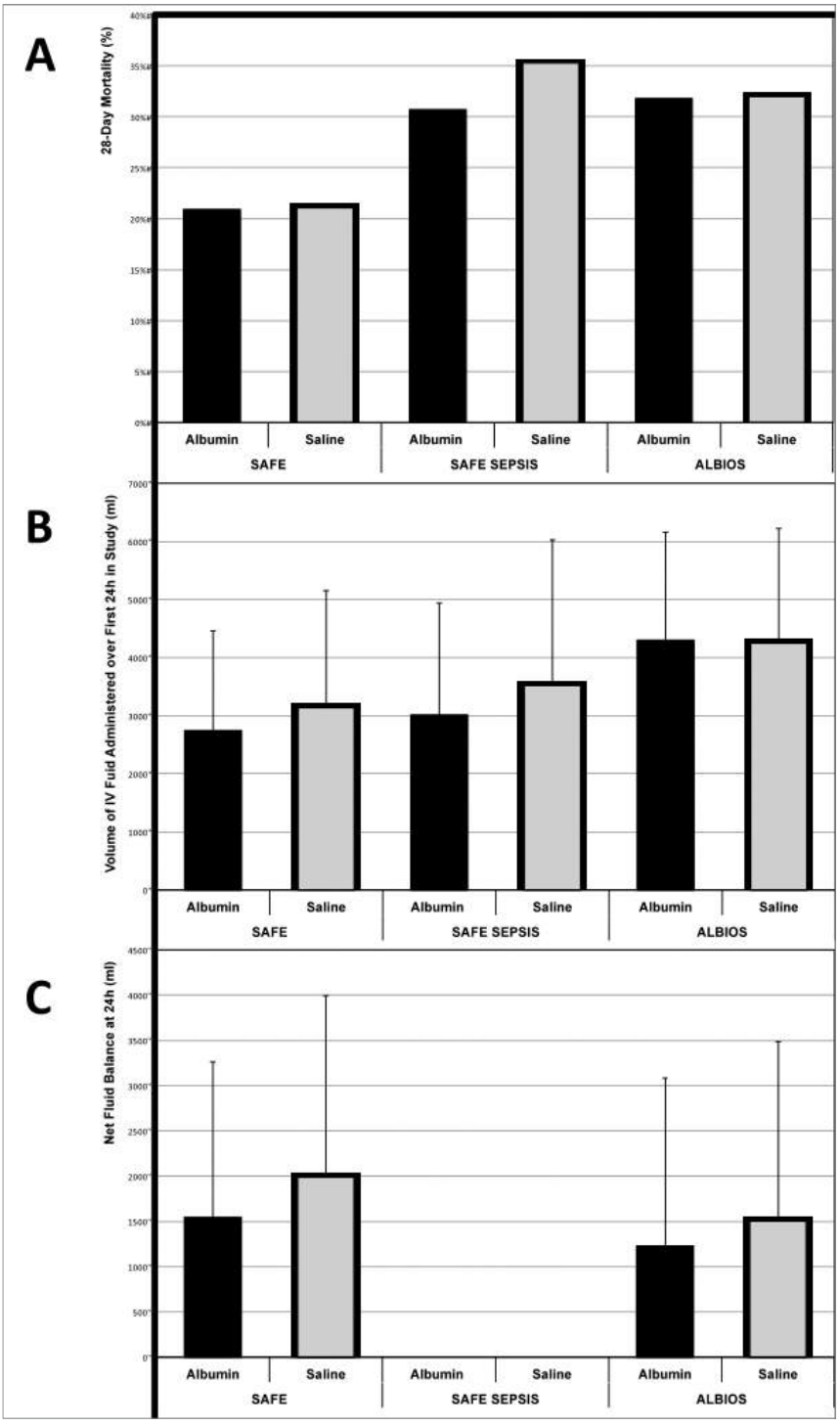

Figure 3. Graphical Representation of the 28-Day Mortality and Fluid Administration and Accumulation in the First 24h of the SAFE and ALBIOS Trials

A: 28-day mortality; B: Total intravenous fluid administration over the first study day; C: Net average fluid balance over the first study day. Albumin: intervention arm; Saline: control arm. SAFE: Saline versus Albumin Fluid Evaluation Study; SAFE SEPSIS: post-hoc analysis of SAFE in patients with severe sepsis; ALBIOS: Albumin Italian Outcome in Sepsis Study. Note: values from the SAFE studies are presented as means, with error bars representing positive standard deviations; values from the ALBIOS trial are presented as medians, with positive error bars derived from crude standard deviation estimations using the interquartile range for comparison. Adapted from Jones et al. (2010); Brown et al. (2001); Roberts et al. (2011)

albumin were administered significantly less study fluid with no differences in transfusion requirements, vasopressor use or need for mechanical ventilation over the first three days of the study, and significantly less fluid overall over the first two days (Finfer et al. 2011). On unadjusted estimate there was no difference in the risk of death between those patients randomised to albumin and those to saline (OR 0.87; 95% CI 0.74–1.02; p=0.09). When adjusted for potential baseline confounding and in the 75.5% of patients with sufficient information, albumin administration was independently associated with a reduction in the odds ratio for death at 28 days (OR 0.71, 95% CI 0.52–0.97, p=0.03) in a model accounting for illness severity, gender, age, postoperative admission, source of sepsis and serum albumin (Finfer et al. 2011).

Importance of Age

The largest trial to date comparing the efficacy of albumin to saline resuscitation in sepsis was not performed in adults, but in critically ill children in sub-Saharan Africa (Maitland et al. 2011a). The *Fluid Expansion as Supportive Therapy* (FEAST) trial was a two-stratum, multicentre, open, randomised controlled study comparing the effects of albumin or saline resuscitation with maintenance therapy only on mortality in more than 3000 children with clinical evidence of impaired perfusion. Children without severe hypotension were randomised to receive 20ml/kg fluid bolus therapy (FBT) of 5% albumin, or 0.9% saline, or no bolus at all, with no invasive ventilation, renal replacement therapy or vasoactive medications available due to the resource-poor setting of the study. Approximately 20% of the study population was recruited following a protocol amendment increasing FBT volumes to 40ml/kg because of concern regarding under-resuscitation compared to international guidelines.

Of the 2097 children randomised to receive FBT, 1050 were assigned to albumin and 1047 to saline, with the groups being well balanced regarding baseline demographics, haemodynamic and clinical characteristics. There was no significant difference in the median volume of all fluid administered over the first, or second, or cumulatively by the end of the eighth hour from the start of

the study (**Table 1**). With reported mortality rates of 10.6% vs 10.5% respectively at 48h (RR 1, 95% CI 0.78-1.29, p=0.96), and 12.2% vs 12% at 4 weeks (RR 1.01, 95% CI 0.8-1.28, p=0.91), and no difference in the incidence of pulmonary oedema, increased intracranial pressure or both at 48h (RR 1.17, 95% CI 0.68-2.03, p=0.49), or the incidence of neurological sequelae or death at 4 weeks (RR 1.04, 95% CI 0.84-1.28, p=0.71), there appears to be no statistically significant difference comparing albumin to saline FBT in this patient group.

However, the most provocative findings of the FEAST trial do not relate to the comparison of albumin with saline, but to the comparison of FBT with no resuscitation, and fully challenge the current paradigm of paediatric FBT-based fluid resuscitation. In this population, FBT with albumin or saline increased the absolute risk of death by 3.3% in children with suspected severe infection (RR 1.45, 95% CI 1.13 to 1.86; p = 0.003). Most deaths occurred within the first 24h, and the majority within 48h. This mortality difference persisted across all pre-specified, pathophysiologically logical sub-groups, with no heterogeneity between centres or across age groups (Maitland et al. 2011a; 2011b).

While it may be difficult to apply the findings of the FEAST trial directly to paediatric patients in ICUs in the developed world, it represents the purest examination of the effects of FBT in isolation in critically ill children to date, and suggests it may be harmful. Despite age-dependent differences in physiology (Gamble et al. 2000), it may be that continuing to compare albumin to other forms of resuscitation fluid in adults is conceptually wrong. Given that the peak haemodynamic effects of such FBT appear to be of limited clinical significance and duration (Aya et al. 2016; Bihari et al. 2013; Bihari et al. 2016; Glassford et al. 2014), perhaps future studies should focus instead on comparisons of any FBT in the critically ill with alternative interventions such as delayed FBT administration or early vasopressor therapy.

Resuscitation vs Supplementation: Does Intent Matter?

As opposed to purely using albumin as a resuscitation fluid, two large RCTs in adults have investigated the role of albumin supplementation and maintenance serum albumin concentration in sepsis (**Table 2**). The *Albumin Italian Outcome in Sepsis* (ALBIOS) study was a large multicentre, open-label, randomised, controlled trial designed to examine the effects of albumin supplementation in more than 1800 patients with sepsis or septic shock across 100 Italian ICUs (Caironi et al. 2014). Patients were randomised to either 20% albumin and crystalloid, or crystalloids alone. Those in the albumin group received 300ml of 20% albumin on randomisation, and subsequent infusions as required to maintain a serum albumin concentration >30g/l. No difference in mortality was observed between groups at either 28 days (RR 1.0; 95% CI 0.87 to 1.14; p=0.94) or 90 days (RR 0.94; 95% CI 0.85 to 1.05; p=0.29), although patients given albumin did have a shorter time to cessation of vasopressor agents (3, IQR:1 to 6 days vs 4, IQR:2 to 7 days; p=0.007).

In a post-hoc analysis of 1121 patients with septic shock, as defined by the Sequential Organ Failure Assessment (SOFA) score, there was a trend towards a reduction in 90-day mortality with albumin administration (RR 0.87; 95% CI 0.77 to 0.99; p=0.049). This persisted when corrected for baseline differences between groups, but not when corrected for what the investigators deemed clinically relevant variables, although the p-value for heterogeneity between patients with and without shock remained significant (Caironi et al. 2014).

The second study, a multicentre, randomised, controlled trial of *Early Albumin Resuscitation during Septic Shock* (the EARSS study) has not been published in its entirety and only an abstract is available (Charpentier and Mira 2011). This is a Stage 4 prospective, multicentre, randomised controlled trial comparing early albumin administration versus saline on 28-day survival in patients with septic shock (*Early Albumin Resuscitation During Septic Shock*, NCT00327704, **clinicaltrials.gov/ct2/show/NCT00327704**). Those randomised to the albumin group were to receive 100ml of 20% albumin every 8h for 72h. Initial findings were reported from 798 patients with septic shock recruited from 29 French centres. No significant difference in mortality was demonstrated between groups (24.1% in the albumin group and 26.3% in the saline group) (Charpentier and Mira 2011). Information regarding the patients in the EARSS trial is limited, and while systematic reviews must account for grey literature (Cook et al. 1993), in the absence of transparent methodology these data must be considered to be at high risk of bias. It is difficult to say how robust the findings of the EARSS study are, without them having been presented in their entirety, or subjected to peer review, but there seems to be little evidence for albumin supplementation improving mortality in sepsis considering these trials in isolation.

In SAFE and ALBIOS the interventions being investigated were quite different. In the SAFE trial, a heterogeneous group of critically ill patients was randomised to albumin or crystalloids for the purposes of volume expansion. In ALBIOS and EARSS patients with sepsis and septic shock were randomised to albumin or crystalloids for the purposes of maintaining serum albumin concentrations above an arbitrary level. All three studies examine albumin administration post-primary resuscitation—patients are enrolled either on admission to the ICU or 6-24h following the development of sepsis within the ICU. Events and exposures in the emergency department, or event in the pre-hospital setting, may confound the results of these studies. In established sepsis, where endothelial dysfunction and glycocalyceal disruption result in increased extravasation of albumin with subsequent tissue oedema, post-primary resuscitation with albumin may not be helpful (Kupr et al. 2007; Woodcock and Woodcock 2012; Margarson and Soni 2004).

A brief report in the *New England Journal of Medicine* suggested that there appeared to be a reduction in mortality among patients receiving albumin that was of borderline statistical significance (RR 0.92; 95% CI 0.84 to 1.00; p=0.046), when the results of EARSS, ALBIOS and SAFE are considered together (Wiedermann and Joannidis 2014). However, it fails to account for this methodological heterogeneity in its pooling of their results. A formal systematic review of 16 trials of human albumin use in adults with sepsis using traditional meta-analytic methodology with the addition of Trial Sequential Analysis (TSA) found no difference in the relative risk

Table 1. Fluid Administered During the FEAST Trial

	Albumin FBT	Saline FBT	No FBT
First hour volume, median (ml/kg)	20 (20—20)	20 (20—20)	1.2 (0—2.5)
Second hour volume, median (ml/kg)	4.5 (1.7—16.2)	5 (1.7—16)	2.9 (0.2—4.2)
Cumulative volume at 8 hours, median (ml/kg)	40 (30—50)	40 (30.4—50)	10.1 (10—25.9)
Proportion receiving blood transfusion	45%	47%	43%

FBT fluid bolus therapy

of death between albumin and control groups, with no evidence of statistical heterogeneity (RR 0.94; 95% CI 0.87 to 1.01; p=0.11, I^2=0%) (Patel et al. 2014). TSA is similar to the sequential interim analysis employed in large phase II clinical studies to account for the increasing risk of type I error with repeated hypothesis testing (Todd et al. 2001) but applied to the repeated testing of significance with the addition of each trial to a meta-analysis (Wettersley et al. 2008). Trials were included if they compared the administration of albumin to a control fluid and presented all-cause mortality data. Published criticisms of this meta-analysis centre on the inclusion of the figures for 90-day mortality from the EARSS trial instead of the 28-day mortality presented in abstract form (Wiedermann 2014a), the inclusion of trials by a group demonstrating a consistent pattern of fraudulent research (Shafer and Wilkes 2014), and the possibility of the inclusion of the same patients from multiple studies (Wiedermann 2014b). However, the meta-analysis appears robust, with multiple sensitivity and sub-group analyses, clearly presented methodology and extensive meta-regression that aim to account for these features (Patel et al. 2014b; 2014c).

Baseline Values: Does Endogenous Serum Albumin Concentration Matter?

In the SAFE trial, no difference was found in mortality between resuscitation with albumin or saline in patients with serum albumin concentrations above or below 25g/l, nor was serum albumin concentration found to interact significantly with the effect of saline or albumin on mortality when considered as a continuous variable (Finfer et al. 2006). Hypoalbuminaemic patients were older, more likely to have undergone surgery, have acute respiratory distress syndrome or sepsis, and less likely to have had traumatic brain injury, though illness severity scoring was similar. The unadjusted ratio of odds ratios between treatment groups when comparing patients with a baseline serum albumin concentration <25g/l and those with >25g/l was 0.80 (95% CI 0.63 to 1.02), with the ratio of odds ratios falling to 0.73 (95% CI 0.55 to 0.97) after adjustment for baseline risk factors for death. However, serum albumin concentration as a continuous variable demonstrated no significant interaction with treatment allocation for 28-day mortality on multivariate analysis. Despite the suggestion of benefit on appropriate adjustment in the binary albumin concentration group, the authors felt that overall this subgroup analysis neither provided significant evidence of a difference in treatment effect of albumin compared to saline resuscitation, irrespective of baseline serum albumin concentration, nor did it suggest that hypoalbuminaemic patients were at an increased risk of death.

While separation in serum albumin concentration was achieved between groups in the ALBIOS study, it aimed to maintain serum albumin concentrations of 30g/l or more throughout admission in the intervention group; this was not achieved until after day 8 (Caironi et al. 2014). Both groups presented with median serum albumin concentrations of 24g/l, though with interquartile ranges suggesting that similar analyses to those performed in the SAFE cohort could have been performed. Baseline albumin concentration is not used to adjust outcomes, nor is it reported as a sensitivity analysis. No post-hoc analyses of ALBIOS study data have been published to date. Unfortunately, no information is available regarding the disposition of the patients in the EARSS cohort as regards baseline serum albumin concentration.

Fluid Administration: Is It a Matter of Volume?

Given the established and increasing concerns regarding fluid accumulation and poor outcomes in a variety of critically ill populations, including those with sepsis (Bouchard et al. 2009; Grams et al. 2011; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network 2006; Payen et al. 2008; Rosenberg et al. 2009; Toraman et al. 2004), the volume of product administered, and the volume of fluids co-administered must be considered as potential confounders when assessing the effects of albumin administration or resuscitation on mortality (Bagshaw and Bellomo 2007). Indeed, the potential to limit the volume of fluid resuscitation is one of the attractive features of albumin resuscitation, and colloid use in general. Standard teaching that 3 times the volume of crystalloid is required to achieve the same effect as for a given volume of colloid has been shown to be incorrect, with the SAFE trial suggesting that, over the first 4 days of the study, 1:1.4 times the amount of albumin to saline was administered. Those in the albumin group of the SAFE trial received approximately 2700ml of intravenous fluid over their first 24 hours in ICU, while those in the saline group received approximately 3100ml. Net mean positive fluid balances at 24h were approximately 1540ml and 1990ml respectively (Finfer et al. 2004). In the 1,218 patients with sepsis, net fluid balance was not reported, but less fluid was given over the first 24h and 48h of the study in the albumin group (603 patients) than the saline group (615 patients) (**Figure 3**) (Finfer et al. 2011).

In the ALBIOS study, both groups received approximately 4300ml of intravenous fluid over their first 24 hours in ICU, with 20% albumin only accounting for approximately 7% of the total fluid administered in the albumin group. Patients in the albumin group reported a net median fluid balance of 1229ml at 24h and 350ml at 48h, while those in the crystalloid group received approximately 4250ml of fluid over the first 24h and had net median positive fluid balances of 1504ml

Table 2. Summary of the SAFE, ALBIOS and EARSS Trials

Study	Author Year	Study Type	Aim	Location	Population	Intervention	Vasoactive Drugs (%)	IPPV (%)	PRC transfusion (%)	CRRT (%)	Mortality
SAFE	Finfer 2004	RCT	To test the hypothesis that there is no difference in 28d mortality between ICU patients given 4% albumin and those given 0.9% saline as resuscitation fluid.	16 closed academic tertiary hospital ICUs in ANZ.	6997 adults; 1218 patients with sepsis or septic shock. Exclusions: imminent death; burns, cardiac surgery and liver transplantation patients.	Allocated fluid to be used for all fluid resuscitation until death, discharge or day 28 after randomisation. Clinician-initiated fluid expansion supported by one or more of: HR>90bpm; SBP<100mmHg or MAP<75mmHg or 40mmHg ↓ from baseline; CVP<10mmHg; PCWP<12mmHg; SBP/MAP Δ >5mmHg with respiration; CRT>1sec; UO<0.5ml/kg for 1 hour or more.	Not documented.	A: 63.8% S: 64.8%	Not documented.	A: 1.3% S: 1.2%	A: 20.9% S: 21.1% SEPSIS A: 30.7% S: 35.3%
EARSS	Charpentier 2011	RCT	To investigate if early administration of hyperoncotic albumin reduces mortality in septic shock compared to saline.	29 hospital ICUs in France	798 patients with septic shock. Exclusions: obesity, severe heart failure, neutropenia, cirrhosis/primary peritonitis, severe burns.	Randomised to Dextran 70, Gelatine 3%, RL and NS solutions. All patients given 20ml/kg over first hour then 10ml/kg over the subsequent hour. Additional fluid: as per treating clinician from end of hour 2.	Not documented.	Not documented.	Not documented.	Not documented.	A: 24.1% S: 26.3%
ALBIOS	Caironi 2014	RCT	To assess the effect of albumin administration compared to crystalloids in patients with sepsis on mortality.	100 hospital ICUs across Italy.	1818 adults with sepsis or septic shock. Exclusions: imminent death; head injury, heart failure, condition requiring albumin administration.	Allocated fluid to be used for all fluid resuscitation until death, discharge or day 28 after randomisation. Following randomisation Albumin group given 300ml 20% albumin; thereafter given 300ml (if albumin <25g/l), 200mg (if albumin 25-30g/l) or no (if albumin >30g/l) 20% albumin daily to maintain serum albumin concentrations above 30g/l. Albumin group allowed crystalloid at clinician discretion. Emergency administration of albumin allowed in Saline group.	Noradrenaline A: 56.2% S: 59.1% 2 or more on d1 A: 28.4% S: 32.1%	A: 78.5% S: 81.3%	Not documented.	A: 24.6% S: 21.4%	A: 31.8% S: 32%

PRC packed red cells IPPV invasive positive pressure ventilation CRRT continuous renal replacement therapy ICU intensive care unit; ANZ Australia and New Zealand HR heart rate SBP systolic blood pressure MAP< mean arterial pressure CVP central venous pressure PCWP pulmonary capillary wedge pressure SBP/MAP Δ systolic blood/mean arterial pressure variation CRT capillary refill time UO urine output A albumin/intervention group S saline/control group.

at 24h and 620ml at 48h (**Figure 3**) (Caironi et al. 2014).

Compared to those in the SAFE trial, the patients in the ALBIOS study were older, had higher illness severity scores, and were more likely to be ventilated, to have received pre-randomisation colloid, and to die within 28 days. These differences may partially explain the differences in volume status. While not significant, lower mortality rates were reported in the intervention (albumin) groups, as were lower fluid balances and/or lower volumes of fluid administered (**Figure 3**). In neither study were mortality results adjusted for measures of volume status.

Of the four most recent systematic reviews of albumin administration in sepsis, none account for total volume of fluid administered or fluid accumulation as potential confounding covariates (Patel et al. 2014a; Jiang et al. 2014; Rochwerg et al. 2014; Xu et al. 2014). Meta-regression techniques allow the effect of potentially confounding variables on effect sizes to be explored, much as logistic or linear regression does at a trial level (Baker et al. 2009). While several studies examined dose, strength, or concentration of albumin in sensitivity analyses (Jiang et al. 2014; Rochwerg et al. 2014; Xu et al. 2014), one meta-analysis performed extensive meta-regression with a variety of covariates, including volume of albumin administered (Patel et al. 2014a). However, more global measures of fluid administration and accumulation remain unaccounted for.

In a systematic review of trials comparing colloids with crystalloids given for the purposes of resuscitation designed to evaluate the reported crystalloid: colloid ratio, a

volume ratio of 1.5 (95% CI 1.36 to 1.65) was identified on meta-analysis of 36 cohorts across 24 trials (Orbegozo Cortes et al. 2015). On meta-regression, the volume ratio significantly decreased each decade from the 1990s, and significantly increased with increasing concentration of albumin solution, in the relevant sub-group analysis. While SAFE was included, the majority of the reported trials are small, clinically and methodologically heterogeneous, and have been reported over a span of four decades. No account was made for the co-administration of crystalloid in the colloid groups, though this degree of detail is often very hard to obtain from papers more than 35 years old. This interesting study demonstrates the facility with which meta-regression can be used to parse the complexities of data synthesis, but then fails to address the topic of mortality. An alternative approach to assessing the impact of volume status on the relationship between albumin administration and mortality in patients with sepsis may be individual patient data meta-analysis. However, obtaining patient-level data from multiple research groups, from studies performed over decades, in a contentious area of research, would be challenging.

Carrier Fluid and Concurrent Administration: Is It a Matter of Co-Exposure?

The effects of albumin, irrespective of the reason for administration, on patient outcome are further confounded by the concurrent administration of the sodium- and chloride-rich carrier fluid of dilute solutions, making comparisons not between different fluids but between essentially similar fluids and additional colloid. However, the sodium and chloride content of various albumin solutions varies with albumin concentration and country of origin, as does the inclusion of other organic compounds such as octanoate (Kaplan and Kellum 2010). In the ALBIOS and EARSS studies patients received a concentrated solution of 20% albumin (Caironi et al. 2014; Charpentier and Mira 2011), while patients in the SAFE study received 4% albumin (Finfer et al. 2004). The constituents and tonicity are not presented in either the papers or any supplemental material. In a nested cohort study of more than 600 patients from three ICUs involved in the SAFE trial, the volume rather than type of fluid administered was a much stronger predictor of the acid-base and biochemical changes resulting from resuscitation with albumin or saline (Bellomo et al. 2006). It may be that the risks associated with excess sodium (Bihari et al. 2010) and chloride (Yunos et al. 2014; Yunos et al. 2012) administration obscure any benefits of albumin delivery. One potential alternative would be to administer concentrated salt-poor albumin solution as a form of low-volume haemodynamic resuscitation. In a retrospective observational study of 202 patients in an Australian tertiary intensive care unit, 100ml of 20% albumin solution delivered the same haemodynamic improvement as 500ml of 4% albumin solution, but in a volume-, chloride- and sodium-sparing manner (Bannard-Smith et al. 2015).

Concurrent administration of other fluids is potentially an important consideration in any study involving a head-to-head comparison of fluids. Other debates rage within the fluid space: the emerging preference for balanced crystalloid solutions over non-physiological "normal" saline, for example (Glassford et al. 2016). However, the signal for harm observed in critically ill patients with sepsis treated with hydroxyethyl starches (HES) across multiple studies is of particular interest, given the process of care observed in the ALBIOS study (Caironi et al. 2014). Overall, 31.9% of patients in the albumin group were exposed to HES in the 24h prior to randomisation, and 17.5% were exposed to a median of 750ml over at least 24h during the study. Moreover, 33.6% of patients in the saline group were exposed to HES in the 24h prior to randomisation, and 17% were exposed to a median of 1000ml over at least 24h during the study. 90-day mortality (Albumin: 47.8% vs 39.7%; Saline: 52.6% vs 41.7%) and the incidence of acute kidney injury (Albumin: 27.5% vs 20.7%; Saline: 27.7% vs 21.6%) were higher in both treatment groups in those exposed to HES during the study. A proposed individual patient comparative analysis of data from the SAFE and CHEST (Crystalloid v Hydroxyethyl Starch Trial) studies is forthcoming, and may offer some insights into the impact of starch exposure in the setting of albumin administration (Hammond et al. 2014), but given these results, post-hoc analyses of the ALBIOS data would provide additional relevant data.

Alternative Approaches to Analysing the Evidence

Bayesian frameworks offer an alternative method by which to analyse the relative comparative effectiveness of albumin as a resuscitation fluid in sepsis.

Network meta-analysis is a non-frequentist method of comparing multiple treatments directly within and indirectly across RCTs. The process is similar to bootstrapping, with a number of iterations being modelled. Techniques to minimise the effect of initial values on the posterior inference and reduce sample autocorrelation are applied (Hamra et al. 2013). In a recent network meta-analysis of fluid resuscitation in 19,000 septic patients across 14 studies with 15 direct comparisons, a lower mortality was associated with albumin use than with crystalloid or starch use in a 4-node model, and with albumin compared to saline in a 6-node model with moderate confidence in all albumin estimates (Rochwerg et al. 2013). Beyond the difficulty of interpreting these results in a frequentist paradigm, bias is of even more significance in network studies than in conventional meta-analyses as it affects not only direct comparisons, but also any indirect comparison made. Clinical, statistical and methodological heterogeneity, and inconsistency, or a discrepancy between direct and indirect comparisons, may affect different regions of a network to a greater or lesser extent (Li et al. 2011). More research is required before the conclusions of network meta-analysis form the basis of changes in clinical practice, but they offer an exciting alternative to traditional models of evidence integration.

Conclusions

Although albumin has been used clinically for more than seventy years, and more than a decade has passed since the publication of high-level evidence of its safety, its administration remains controversial in the critically ill. Randomised, controlled trials demonstrate no benefit from the routine correction of hypoalbuminaemia in this population. It is unlikely that subsequent large frequentist RCTs of albumin-based FBT in specific patient populations will be performed, given the difficulty in identifying such patients, the number of patients to be recruited to power such a study, and the prohibitive cost of providing and packaging solutions and

placebos on such a scale. In Australia, where albumin is provided to hospitals as blood product at no cost by the Australian Red Cross Blood Services, a possible solution would be to employ a Bayesian platform trial (Berry et al. 2015). With this methodology it may be possible to compare different concentrations of albumin, in different sub-groups of patients, with different colloid and crystalloid solutions. As with network meta-analysis, this is a novel and attractive approach to trial design, but it is likely to be several years before the suitability of such a methodology can be assessed, with the first such trial only just receiving funding (Monash University School of Public Health and Preventive Medicine 2015).

Outside of those populations in which its use is contraindicated, such as TBI or burns, the current evidence base demonstrates that the administration of albumin as resuscitation fluid to critically ill patients is safe, and may be beneficial in patients with severe sepsis. If any benefit is to be seen with albumin use, it will be in subgroups of critically ill patients, not in the undifferentiated population of the ICU, and use will be dependent on regional and local guidelines, economic concerns and clinician preference. At present, clinical judgement and physiological reasoning, rather than strength of evidence, remain the primary drivers for the administration of albumin in the critically ill. ■

Acknowledgements

The authors would like to thank Dr. Craig J. French, Dr. Maurice Le Guen, Dr. Stephen Thornhill, and Dr. Mark Kubicki for their advice with the preparation of the final manuscript.

Financial Disclosures

RB has received unrestricted research grants from Baxter Pty Ltd.

Funding/Support

The Avant Doctors-In-Training Research Scholarship supports Dr Glassford. This study was supported by an unrestricted educational grant from the Austin Hospital Anaesthesia and Intensive Care Trust Fund.

Role of the Sponsor

Avant and the Austin Hospital Anaesthesia and Intensive Care Trust Fund played no further role in the preparation of this manuscript, nor had any role in the design and conduct of the study; collection, management, analysis, or interpretation of the data beyond that described; nor any role in preparation, review, or approval of the manuscript.

Competing interests

The Avant Doctors-In-Training Scholarship funds NJG's research salary. RB has received unrestricted research grants from Baxter Pty Ltd.

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The Power of Listening

Engaging the Consumer

Darryl O'Callaghan and Julie Vermeir are survivors of a road trauma that happened in 2010. Their article provides insight into their journey as patient and wife, and the lessons that can be learnt.

Darryl's Story

There are many courageous souls who have lost their lives attempting to climb Mt Everest. Those who attempt such a climb arrive at the foot of the mountain after many years of preparation and training. They are extremely fit, possess all the best climbing gear and have an experienced support team. Yet there is still no guarantee they will make it to the summit, just as there is no assurance that they will not lose their lives trying.

When I woke up in the intensive care unit (ICU) after three weeks in an induced coma, I didn't realise at that time that I was at the foot of my own Everest.

I had been involved in a head-on motorcycle accident with a wayward car trailer, and sustained catastrophic injuries. The right side of my body was largely crushed. I had sustained a collapsed right lung, badly bruised left lung, fractures to 12 ribs, a tear to my right atrium, multiple fractures to my pelvis, a shattered right shoulder, internal organ damage, and the list went on. I was barely clinging to life.

On the day of the accident, doctors and surgeons worked tirelessly on me for many hours, yet despite all their efforts, they were still struggling to keep me alive. That evening they told my family that due to the extent of my injuries they did not expect me to survive the night.

I did survive, but now a torturous physical and mental journey stood before me. With no training, a severely broken body and no mental preparation, I was going to have to climb my own mountain. It was the first time in my life that I truly understood why people lose their will to live. Every day, my body was in a battle, in a war that appeared impossible to win.

As if my injuries were not bad enough, I then contracted pneumonia and sepsis while in the ICU. I was running an extremely high fever from the infection and my body felt like it was always on fire. I had absolutely no strength left to fight, and what was I fighting for anyway? I was paralysed by drugs and could not move. I had no idea if I would have any kind of quality of life if I made it out of the ICU. How easy it would have been for me to simply give up. But I had a wife and a baby daughter. They gave me purpose and a reason to live.

I made it out of the ICU after 35 days of enduring what I could only describe as sheer physical and mental torture. But this was only base camp. I still had a huge mountain to climb, one which would require every last ounce of determination and mental strength I had, because physically I was spent.

Julie's Story

Ascending a virtual Everest is not just a journey for the patient; it is also one the patient's family must undertake. The moment they receive that phone call telling them that their loved one has been involved in an accident, their lives are changed forever. Like the initial trauma victim, family members have not trained for such a journey—one which is filled with high levels of stress and anxiety that seem not to subside for days, weeks, even months on end, until they know their loved one is out of danger. These emotional challenges are often accompanied by physical symptoms, such as loss of appetite, tension headaches and insomnia. Despite undergoing their own trauma, families are often not recognised and treated as traumatised victims themselves. They are merely regarded as family members of a patient.

When Darryl's accident occurred, we had only been married for three years and we were first-time parents of a 10-month-old girl named Siana. Each day I would sit beside Darryl's ICU bed praying that his condition would improve and that my daughter would still have a father. For many weeks, I did not know if he would survive. He underwent a barrage of operations whilst in an induced coma and every day was the same: one moment he appeared to be improving, the next it looked like his body would succumb to the catastrophic injuries it had sustained. Although he was the one with all the broken bones, I was the one with the breaking heart and a head that was being compressed by the enormous stress I was under. Despite the gravity of the situation, I was not recognised as a traumatised victim, and society expected me to return quickly to my normal duties. I was to make sound decisions about my husband's treatments, look after my daughter and return to work so that the bills could be paid, all without missing a beat.

What got me through each day was my faith in God and the support of family and friends, many of whom were also dealing with their own symptoms of trauma, particularly Darryl's family. From a hospital perspective, we were just "bed 22's family", and nobody was there to provide us regular counsel and help us climb that mountain. Such help would have been welcomed, especially in the early days when we were summoned by doctors to attend family meetings. We dreaded those meetings, as we had seen other families come out of them absolutely shattered, leaving us to

believe that a meeting was a sign of bad news. Indeed we often did not know the nature and purpose of the meetings, which created further uncertainty, adding to the enormous stress we were already under. This, coupled with the fact that we each held a different perspective, made it difficult to process the information adequately. We would hear the same words and yet each of us would have a different interpretation of what was said.

Pathways in Trauma Survival

We would suggest there are two pathways in trauma survival: the one the direct victim of trauma takes, and the one family and friends take (often the journey of the 'silent victim'). The challenges can be similar, but at the same time quite different. The patient has to overcome the enormity of dealing with the physical aspects, which may include serious injuries or sickness, or both. There is also the mental challenge of dealing with the environment of an ICU facility, feeling scared and alone, and dealing with the uncertainty of what lies ahead. These physical and mental challenges continue beyond the ICU walls, often intensifying during major transitions, such as from the ICU to the ward, to rehabilitation and moving home. Making it home is far from the end of the journey for many patients. It is simply another stage camp on their gruelling climb back to hopefully something of a normal life.

Family members on the other hand are confronted with an out-of-control rollercoaster ride of emotions. They have to grapple with the initial shock of their loved one's condition as well as navigate their way through a medical labyrinth of ICU equipment, jargon, treatments, forms, numerous medical staff, and even sometimes police and lawyers. They have to deal with all this while their normal life commitments go on. The bills keep coming, work still needs to be attended, children need to be cared for and schooled. However, there is less time, and possibly less or no money coming in if the primary income earner is the one in the ICU. The family effectively has to go into their own survival mode simply to get through each day.

Despite this, do hospital staff treat these people as trauma victims? Our experience was no. Families are largely left to fend for themselves. It's not because hospital staff do not empathise with them or are unwilling to help, but rather because they have limited capacity. In such a context, it is clear that hospital resources get directed to the person who is most at risk of dying—the obvious trauma victim.

The Opportunity

This is only a small insight into the incredible challenges and pressures faced by patients and their families. We could write a 30-page article and still only touch the surface of the journey we undertook. Until we travelled that path ourselves, we had no real appreciation as to the enormity of the difficulties posed by a catastrophic trauma, and the incredible courage, strength and resilience all who are involved must have to conquer the mountain of adversity that such a trauma throws at us.

> **"making it home is far from the end of the journey for many patients"**

As the saying goes, "if you truly want to understand someone's perspective, walk a mile in their shoes". Obviously, this is not practical when it comes to experiencing a trauma caused by something such as a road accident, and that is why we believe consumer engagement is so important. It may well be one of the missing pieces of the jigsaw puzzle for many medical teams in their never-ending pursuit to improve outcomes not just for patients but also their families.

Survivors of trauma are truly the custodians of a wealth of knowledge that should never be wasted. For it is people like us who truly understand what the climb to Everest is like. Mountaineers attempting to climb Mt. Everest will engage the services of people who have climbed the mountain before, to learn as much as possible, so that their chances of success can significantly improve. So why would medical professionals not also prepare in the same diligent manner, by asking trauma victims for guidance on what can be done to improve the outcomes for those unlucky enough to follow in similar footsteps. By gaining such valuable insight, medical professionals would be far better equipped to support patients and their families in making their ascent up that mountain.

The Consumer Experience

We have been consumer representatives in a large hospital in Brisbane, Australia for the past 18 months, and during that time we have been pleasantly surprised by the eagerness of medical teams to accept us into their various committees. We've been welcomed to sit alongside senior doctors, nurses, allied health professionals and members of hospital executive staff and provide our input into decisions. However, we have also observed that for some people engaging the consumer is more of a box ticking exercise, to say the consumer's perspective has been sought. For others, the role of the consumer is seen as an important piece in creating a more holistic picture of how to care for patients and their families.

We expect service lines that seriously engage the consumer will see a step change in the way they deliver their services. However, others will meanwhile continue along the same path they have trodden for some time, never truly understanding the missed opportunity.

The Challenge We Propose to You

The questions for all medical professionals, in particular ICU medical staff, are simple: do you truly know what it is like to lie in an ICU bed fighting for your life? Do you know what it is to sit in a waiting room day after day, night after night, not knowing whether your loved one will survive? If the answer to these questions is yes, you have an insight that many do not. We would be very surprised if that experience did not in some way change your thoughts on how medical services should be delivered. If you have no such insight, then what have you to lose by engaging with the consumer? Maybe a little of your time; but in return, it may just be an eye opening experience that changes the way you practise medicine forever. A change that will hopefully enable you and your colleagues to help ease the horrific and arduous ascent up a mountain that no patient or family would ever consciously choose to travel. A change achieved through the power of listening! ■

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Improving Healthcare

The Role of the Human Factors Specialist

What is human factors? How would you explain to a hospital director why they should hire human factors specialists?

Human Factors (HF) is the study of how people interact physically and psychologically with their environment—this includes the products, tools, procedures and processes they interact with. HF professionals use insights about human limitations, cognitive biases and social interactions to inform the design of clinical environments, procedures and medical devices. We also inform the selection and implementation strategy for products to purchase and use in clinical environments. HF engineering in healthcare aims to improve patient safety, minimise use errors and reduce training time associated with electronic systems, medical devices and compliance with procedures. For example, in some cases clinicians resist adoption of electronic health records (EHRs), leading to documentation workarounds or missing critical patient information. Traditionally, when we look into the reasons for this behaviour the finger has been pointed at the people at the sharp end; and the solution has been to require more vigilance. But the truth is that there are a number of factors beyond individuals, which are systemic factors that contribute to these kinds of problems and to patient safety incidents. HF experts are trained to identify systemic factors and to develop solutions and risk mitigations that address the root causes of such problems. An HF expert would go into the clinical environment to identify the barriers to adoption or compliance through the collection of objective data. With EHRs, the patient care documentation or medication ordering may require too many steps in a sequence that is not intuitive; or the EHR may not be well interfaced with other electronic systems, creating the need for additional data entry into multiple systems. Users may decide that documenting on paper is much faster and easier for them and their busy schedules, than having to go through many steps and trying to think about the order of steps that is not intuitive to them. If we think of hand hygiene compliance, soap and hand sanitizer dispensers may be positioned inconsistently in different rooms in a hospital, which could result in preventing clinicians from properly performing hand hygiene. An HF expert would identify such barriers to effective and efficient work, and then help the hospital develop mitigating solutions that improve such systems issues, rather than ask individuals to be more vigilant. Asking individuals to be more vigilant is essentially asking them to compensate for deficiencies in the system. However, the inherent risks in the system remain.

> **“Asking individuals to be more vigilant is essentially asking them to compensate for deficiencies in the system”**

How does Healthcare Human Factors work with University Health Network in Toronto?

Our team is embedded within the University Health Network (UHN) and we work with all the affiliated hospitals on improving patient care and safety. Human Factors is part of incident investigations, process and quality improvement, as well as staff and leadership training. Additionally, one unique area of work we do is support for procurement decisions of safety-critical equipment, such as infusion pumps, EHRs, patient monitors, ventilators, etc. The decision to purchase technology is a huge investment, and hospitals buy only once every ten to fifteen years. The decision traditionally has been based on cost and functionality. We worked with UHN to change that model by including HF as part of the decision-making processes. We, HF specialists at UHN, evaluate the contender products in a way that provides objective data acquired through simulations with UHN staff—those people who will ultimately care for our patients with the technology. We engage all the stakeholders, and in a simulated environment test the shortlisted products to identify any use-related and safety issues relevant to how the technology will be implemented in our organisation. It often happens that the vendor provides a nice demonstration and impresses everyone to think they sell a great piece of equipment. Then, when we do the user evaluation and ask clinicians to perform essential tasks with that equipment, we find that they commit a lot of safety-critical errors that are facilitated by the design of the technology. The objective evaluation data provides the evidence to inform the purchasing decision. The data directly informs the negotiations with vendors about customisations that are required if we purchase a specific piece of technology. It also informs the implementation strategy. After we purchase equipment, the insights about the shortcomings of this piece of technology help us design procedures and mitigations around those known shortcomings.

For the user testing simulations, we focus on the interaction with the devices while we maintain high fidelity of the clinical environment. If we are testing a ventilator, we would bring in a nurse or respiratory therapist and have them perform a basic patient setup and programme the breathing protocol. Actors would play other patients asking for help on the next beds, and a confederate nurse would interrupt the simulation participant in the middle of the programming task. If in real life there is a chance that while you are programming this ventilator, somebody is going to interrupt you, then you have to test the scenario of an interruption, engaging in a conversation, and then having to go back to the task that you left in the middle of programming. Whatever this ventilator has to offer in terms of interface,

we would evaluate how effective it is to support that interruption, because it happens in real life.

We have also evaluated shortlisted medical devices or EHR systems where there was no clear winner; all of the products would perform equally poorly in terms of usability and use-safety. The hospitals would come to the conclusion that the existing technology is not significantly better than what they already use on the patient floors. In these cases the hospitals may decide to defer the purchase until the next generation of this type of technology is developed to hopefully address use-related issues.

We also engage in incident investigations. We help analyse what happened and identify the contributing factors, while ensuring that we look at the whole system. Then we facilitate a process to design risk mitigations that will remove the identified risks. This is a process of iterative design either through simulation or within the actual clinical environment. Additionally, we look at how we can improve incident reporting and help with process improvement, looking for barriers and latent safety factors.

Finally, we also have an educational role, and have been providing training to frontline staff and leadership on the basics of HF for a decade now. By educating staff at the sharp end about human factors, we don't expect them to change the system, but to change the way they view their environment. The next time a nurse or a physician is faced with having to make a decision based on incomplete patient information, they would question why they are in this situation, and ask if something can be improved in the process or environment. The HF education serves to change people's perspective on their environment and help them recognise systemic issues. They would employ critical thinking and identify issues. They would then engage us to confirm and refine the focus on the factors that contributed to the issue, so that we can help them improve the process and design mitigations.

How can human factors specialists help in the very complex intensive care unit environment?

Addressing complexity is at the heart of HF work. An HF expert would identify HF and systemic issues in an ICU and develop mitigations. These could be organisational, process, team, environment, technology or cognitive issues. HF experts could start with a contextual enquiry, including observations, stakeholder interviews and focus groups, to identify the issues and their root causes. Usually when you go into an ICU or other clinical environments, people have a sense of what the problems are, but not necessarily what the root causes are. Once these are identified, HF experts would develop solutions and risk mitigations that will be iteratively tested with the clinicians and other stakeholders to make sure that they work for them, in their environment and in their specific process. The testing of the solutions would be conducted either in a high-fidelity simulation environment or in the actual clinical

setting, and the HF expert will refine the solutions until a positive effect is confirmed.

HF professionals can help improve patient safety, workflow, processes, procedures, tools or the physical environment such that people can use these most effectively; for example: designing user-friendly order sets, procedures around the use of such order sets, effective paper and electronic forms, as well as the selection and implementation of medical devices (such as infusion pumps, patient monitors or ventilators), personal protective equipment, etc.

HF experts can also inform the improvement of non-technical aspects within an ICU such as communication and teamwork issues. In the last few years, these have been major contributing factors to adverse events. ICUs are starting to appreciate the importance of investing in improving team members' soft non-technical skills so that the ICU environment can become more effective, efficient and safer.

How can human factors alleviate staff issues such as fatigue and burnout?

With fatigue, we would follow a similar process to that described above, to identify what is causing the fatigue. We know a lot about the effects of fatigue as a human limitation. When someone comes to us and says that they are experiencing staff fatigue in their unit and it's affecting the quality of care, as HF experts we wouldn't look at the symptoms of the behaviour, but we would identify what is causing the fatigue: Are staff moving around the unit too much? Is the current layout of the unit the problem? Is the way things are organised the problem? Are there very long shifts or too much clutter in the unit? Sometimes physical clutter or noise levels in an environment create high cognitive load in an already demanding setting like the ICU. We need to determine the root causes and appropriate solutions to address them. The goal of HF is to design an environment that takes into account human limitations—to do that, HF experts identify and mitigate systemic issues within the environment in which humans are interacting, functioning and working.

With regards to burnout, we need to go a step further and design the user/human experience. This is the process of enhancing people's satisfaction by improving usability, ease of use, the pleasure that they experience through interaction with their environment. This goes beyond addressing the human limitations and is more on the emotional, experiential side—producing a positive experience triggered by interaction with the technology that people use, the processes they follow, the teams that they participate in. Part of this is a design and engineering challenge, but it also involves the organisational culture.

How can human factors specialists reconcile the different viewpoints in healthcare to bring the best results?

HF experts are very careful to separate opinions and preferences of stakeholders from objective data. HF uses a rigorous investigation and design methodology to acquire objective data and engage all relevant stakeholders. We find that people's preferences and opinions don't always reflect how they perform. For example, when we evaluated the ease of use and safety of several infusion pumps, we engaged purchasing decision makers, technology manufacturers, IT managers, clinicians, administrative staff and pharmacists in the evaluation. We found that everyone really liked the one pump (Pump A). But when we looked at how people performed the basic safety critical tasks we gave them, we found that people actually committed the most serious safety errors with that pump (Pump A). It was not a safe design, but it appealed to the users because it was similar to what they were currently using; but they did not realise they had committed those errors while using it. During the debrief sessions, when we revealed the errors that they had committed, stakeholders appreciated the risk that this pump introduced and supported the purchase of the other contender product (Pump B).

You have worked on effective clinical tool design with the emergency department at UHN (Taneva and Chagpar 2013). Please explain the process.

We worked on a decision support tool for diagnosis of community-acquired pneumonia. We did a heuristic evaluation to identify basic usability issues, such as if there was too much information and clutter. We also looked at how the information is organised—if it was logical and if it allowed easy scanning. We went into the emergency departments of three different hospitals, and did observations and interviews with end-users to identify the critical information sets and decision points they used from all the information presented in the tool. That way we found out what information was really important to them and what helped them make a decision to diagnose community-acquired pneumonia. We were able to reduce the content to only what is critical for the decision-making. We reduced the clutter and kept only the high-priority information that directly helps make the diagnosis. Then, I worked with a visual designer to redesign how the content is presented. We reduced a five-page information sheet to one page and a half, where the most important information was on page one. We validated the designs with the end-users and the tool is now used throughout the Greater Toronto area.

This issue of ICU Management & Practice has a cover story on personalised medicine. What are the lessons from systems thinking for precision and personalised medicine?

The clinical environment is very complex right now. The amount of information and communication has become a major contributory factor to adverse events, people dying. Precision medicine is about to exponentially increase the amount of information and communication related to patient care. If we continue to focus on the sharp end and ask people to be vigilant, it's not going to get better. We need to recognise that safe, reliable systems and processes should be our focus in order to be ready to brave the challenges of introducing precision medicine. Then we will have a chance to be successful. Precision medicine is a very exciting field, but we have to make sure that as a culture and as an organisation we are mature enough to approach it in the right way. We need to think in systems terms and be mindful of human limitations. With this approach we can reduce the frequency and the consequences of errors when we introduce precision medicine. ■

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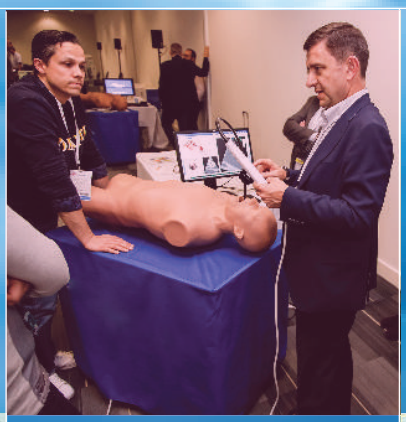

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Professorial Clinical Units

Advancing Research in the Intensive Care Unit via the Integration of a Nursing Professor

Advances in healthcare and management strategies for the critically ill patient continue to evolve at a rate that can become challenging for individual clinicians to keep abreast. It is crucial that medical, nursing and allied health professionals use an evidence-based practice (EBP) approach to support these advances and translate research evidence to practice. Barriers to research and EBP have been identified as lack of time, lack of authority, unsupportive organisational infrastructure, lack of access and lack of confidence in performing critical research appraisal (Hutchinson et al. 2006). Further, it has been highlighted that nursing research activity in the speciality of intensive care may be low in comparison to other disciplines such as medicine, and that generally nurses may be ill-prepared to be active consumers of research let alone undertake research studies (Bucknall et al. 2001; Makic et al. 2011; Smith et al. 2016). However, the days of respective disciplines working in silos are surely long over. It makes sense that different healthcare disciplines work together in a collaborative united manner to foster a unit culture of EBP and active research. Here, we outline the strategies undertaken in our intensive care unit (ICU) to ameliorate this challenge and highlight the positive outcomes we have achieved.

Background

The Royal Brisbane and Women's Hospital (RBWH) is a major metropolitan quaternary public hospital in Queensland, Australia. The Intensive Care Services (ICS) in this hospital admit over 2400 patients per annum. The ICS consists of the intensive care unit (ICU) itself, plus outside services such as end-of-life consultations, central venous access line services, hospital-wide medical emergency responses and telemedicine outreach ward rounds. Patients admitted to the ICU are high acuity, and common medical diagnoses include: acute neurological disorders and trauma, respiratory diseases, renal dysfunction, burns, sepsis (including bone marrow transplant-related infections) and multi-trauma injuries. The unit is divided into four independent areas called pods, each with nine bed spaces. The operational capacity is 36 critically ill patients. However, one pod is allocated to short-stay, postoperative, high-dependency admissions and not included in the current funding for 26 ICU beds.

Supporting this sizeable ICS infrastructure is a large number of staff. The actual ICU is staffed with a Medical Director, who also serves as the ICS Director of Research, 10 Staff Specialists, 13 Senior Registrars and 21 Registrars. From a nursing perspective, the ICU is managed by an Assistant Director of Nursing, three Clinical Nurse Consultants (CNCs), two Nurse Managers and two Nurse Educators. There are approximately 204 registered nurses (RNs), who deliver, and are responsible for, complete patient care in a ratio of one registered nurse (RN) to one mechanically ventilated patient. There is a supernumerary CNC or Clinical Nurse-in-charge of the ICU on each shift. Additionally, there is one supernumerary registered nurse (RN) acting as clinical coordinator in each pod for each shift across 24 hours and one registered nurse (RN) acting as clinical support who is also supernumerary and supports the bedside RNs across two pods. An additional RN is allocated to the medical emergency response team to attend emergencies throughout the hospital, but this role also provides additional ICU clinical support in the pods where most needed when not attending emergencies.

Challenges

The ICU nursing leadership group has long recognised the challenges in promoting EBP and an active research culture and has explored options to facilitate continued professional recognition and intellectual growth of nursing staff. Over time the ICU nursing team implemented a range of strategies and these included: expectations of research and EBP in nursing role development and position descriptions, monthly nursing research and education forums, journal club, engagement with a hospital-wide EBP training programme, localised quality improvement strategies leading to small research projects and conference presentations and local, national and international conferences. However, there was little nursing research emanating from this potentially fertile area.

The dilemma of how to progress an active and vibrant research culture in the ICS that must be effective and sustainable is ever present. The ICS at RBWH has a strong research focus, led by Professor Jeffrey Lipman, primarily through the Burns, Trauma, Critical Care Research Centre, School of Medicine, University of Queensland (**btccrc.centre.uq.edu.**

Figure 1. The Intensive Care Nursing Professorial Unit sign

au). This University Centre publishes over 100 peer-reviewed papers per year and has crossed the "usual" hierarchal domains of medicine, surgery, clinical pharmacy and physiotherapy by establishing and building cross-discipline collaborations. Historically, nursing research in the ICU began with a relationship with a university partner that centred primarily on postgraduate education i.e. critical care nursing certification. Up to 2011, small pockets of nursing research were undertaken; however, this was always under a model hampered and frustrated by insufficient resources, lack of funding, staffing, time and even acknowledgement.

Recognising these impediments, the ICU nursing leadership group was in accord that the ICU RNs were passionate about the quality of care they provided to critically ill patients, and would move towards a higher level of direct involvement in leading EBP and research in intensive care nursing care if adequately supported and mentored. This meant raising the bar in the intensive care nursing team to identify, support and drive intensive care nursing and multidisciplinary research.

A Way Forward

The term professorial unit exists globally in the titles of many clinical and academic staff from a variety of departments e.g. Surgical Professorial Units, Professorial Unit of Surgery, Medical Professorial Unit etc. However, in reality what does this mean? Professor Glenn Gardner, inaugural Clinical Nursing Chair, Queensland University of Technology (QUT) and Director of the Centre for Clinical Nursing, RBWH, conceptualised and implemented the foundational nursing professional unit (NPU) over 12 years ago in a surgical ward at the RBWH. The NPU was established as an innovation to strengthen university/health service collaboration and to build and promote a clinical nursing research and EBP culture. There are now four successful QUT Nursing Professorial Units at the RBWH: kidney health, cancer services, mental health and intensive care.

Building on the NPU model founded by Professor Gardner, in late 2011 we established the Intensive Care Nursing Professorial Unit (ICNPU)—a unique collaboration with healthcare providers (ICS, RBWH) and academia (School of Nursing, Queensland University of Technology as the university partner). The QUT/RBWH ICNPU is a strategic direction to progress an active and vibrant intensive care nursing and multidisciplinary research programme in the nursing team. This model is a partnership between clinical nursing leadership, academic leadership and clinicians to advance the influence of high quality nursing care on patient outcomes. The ICNPU aims to provide high-level support for optimum continuing professional development of nurses and research to inform nursing practice in a specific clinical environment.

To achieve this the ICNPU supports the professional development of intensive care RNs through active engagement in EBP and research by:

- Developing an active intensive care nursing research culture within the service
- Demonstrating nurse-led research
- Developing research skills of intensive care nursing staff
- Creating opportunities for collaborative research projects (including multidisciplinary research)
- Providing mentorship for intensive care nurses undertaking tertiary studies
- Providing guidance and support for grant applications

> **progress an active and vibrant research culture in the ICS**

At inception the ICNPU used an embedded scholar model whereby an academic (Professor of Nursing) was located in the ICU one day per week. The ICU provided infrastructure, support and access. This was an unfunded model with academic time provided as 'in-kind' by the university. We held a joint meeting of nursing leadership with Kidney Health Services to develop a vision statement. The ICNPU vision statement is "providing optimium patient care through research and evidence-based practice". We placed the vision statement proudly on a sign at the entrance to the ICU (**Figure 1**), representing our commitment, and the collaborative organisations' (QUT and RBWH) commitment, to ensuring this innovation is effective and sustainable. Further, we developed a strategic plan based on the three areas of continuing professional development, research and evidence-based practice. Each area has agreed goals, actions

or activities and identified outcomes. The strategic plan is used to drive our goals and focus our achievements and is reviewed bi-annually.

In 2015, acknowledgement of our achievements culminated in the creation of the formal position of a full-time Professor of Nursing—jointly appointed and funded between RBWH and QUT – to lead the ICNPU. Further, we have established and implemented a Clinical Nurse Research position to progress EBP goals and work with the Professor of Nursing to drive clinical research. Professor Lipman conducts a weekly collaborative research meeting with research managers, clinicians (medical, nursing and allied health) and academics from three different universities to discuss issues and plan projects.

Thus far we have undertaken six completed clinical projects and trials, have a further seven trials or projects in progress, offered RNs oportunities to participate in research processes, recruited a number of RNs to higher degree research studies, achieved successful higher degree completions, and suported RNs in publishing and conference presentations. Specifically, we have completed a project to scope barriers and enablers to EBP in our ICU. This project will be used as the platform to further implement context-specific EBP and research utilisation strategies for staff in our ICU.

Conclusion

An active research and EBP culture requires organisational commitment of resources, time and support. We have outlined one successful strategy, the creation of an Intensive Care Nursing Professorial Unit, led by a Professor of Nursing—jointly appointed by the hospital and university, and supported by a Clinical Nurse–Nursing Research, to build a strong culture of research in the ICU. ■

Abbreviations

EBP evidence-based practice
ICNPU Intensive Care Nursing Professorial Unit
ICS intensive care services
ICU intensive care unit
NPU nursing professorial unit
RN registered nurse

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The ICU-Hear Project

Introducing Live Music for Critically Ill Patients

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The ICU-Hear project delivered by the charity Music in Hospitals™ provides specialised live music sessions for critically ill patients. The initiative started after Helen Ashley Taylor (a former ICU patient) met Sister Natalie Mason, Adult Critical Care Follow up Lead at Manchester Royal Infirmary at a regional support group for former ICU patients. Helen had volunteered for the charity Music in Hospitals™ for over 7 years. After Natalie and Helen discussed the potential patient benefits of live music on the ICU, a pilot project was set up. A working group now plans to research the positive impact on patient health.

Soothing melodic music regularly meanders through and above the environmental soundscape of the critical care unit at Manchester Royal Infirmary (MRI). From the tranquillity of an acoustic guitar or a gentle African harp accompanied by beautiful soft singing to the flowing, mellow rich tones of a clarinet, professional musicians from the long-established charity, Music in Hospitals™, have been playing live music to critically ill patients since July 2016. The initial pilot project attracted significant attention, including national press and local television coverage (Ashley Taylor 2016; Granada News 2016). In January 2017 the UK Prime Minister acknowledged the work with a Points of Light award, recognising the initiative borne out of patient experience that has resulted in a successful patient and staff collaboration (Prime Minister's Office 2017).

Setting the Scene

It has taken two years for the idea to evolve to this stage of development and recognition, having begun when I experienced being an ICU patient in February 2015. Considerable planning and preparation was involved before the first music session took place, and since then the compelling positive results and patient feedback have continued to inform the evolution and expansion of this project. "*Absolutely brilliant*", "*wonderful*", "*soothing*", "*calming*", "*fantastic*", "*uplifting*", "*enjoyable*", "*relaxing*" "*amazing*", "*beautiful*", "*therapeutic*", "*pleasant*", "*peaceful*", and "*welcome*" are words regularly used by patients to describe the experience. These are not ordinarily adjectives chosen by patients to describe any part of the ICU experience. Relatives also express gratitude for being able to smile and relax on the ICU during what is an exceptionally difficult time in their lives. Indications from feedback and data collected suggest the music may be beneficial to patients' clinical outcomes, relatives and caregivers and the working atmosphere more generally.

> **The beauty and quality of the soothing music were a welcome respite**

Transforming an Anxious Time

These positive self-reports made by patients after hearing live music on the ICU are significant. Many published accounts focus on harrowing ICU patient experiences (particularly of delirium), which remain in former patients' memories for a considerable time. Both qualitative and quantitative data collections have been used during this project, and to date all patients have confirmed feeling relaxed whilst hearing the music. Adult Critical Care Matron Donna Cummings at MRI reports that the relaxing effects of the music on patients continue long after the musicians leave the ward. She describes the musical intervention as "overwhelmingly moving to see and participate in".

This ability to focus on live music is noteworthy considering the prevalence of delirium among ICU patients. There is evidence too that relatives can suffer with anxiety and be at risk of developing post-traumatic stress disorder (PTSD) after witnessing loved ones suffering from critical illness and delirium (Jones et al. 2012). Published reports state that delirium is common and can result in a longer ICU stay, longer duration of mechanical ventilation and is associated with higher mortality rates (Ely 2001). Recognition and early intervention of the management of delirium is important, including the most commonly missed subtype, hypoactive delirium (Meagher 2000)—often called 'quiet' delirium. Sister Natalie Mason and Matron Donna Cummings report that the MRI uses a combination of pharmacological and non-pharmacological strategies to both prevent and manage delirium in patients on the ICU, and the unit has seen dramatic reductions in incidences of delirium over the past 18 months.

Patient Experience of the ICU Sound Environment

I documented my own patient experience after discharge, then my post ICU recovery period 13 months later. Re-reading that first contemporaneous account one year on, after a challenging recovery period and after hearing the experiences of other former ICU patients, I started considering further the potential benefits of offering live music to ICU patients. My own account frequently refers to the noise I experienced 24/7 on the ICU, and the distressing effect it had on me. I couldn't stop the unpleasant cacophony of sounds reaching me. I couldn't lift my arms to put my hands over my ears, and I couldn't always communicate to tell anyone how upsetting I was

Holly Marland -playing the Kora, an African harp, to a patient


Holly Marland with a Kora

Martin Bickerton - guitar


(R-L) Sister Natalie Mason, Holly Marland, Helen Ashley Taylor with ICU staff

Wordle - from feedback forms

finding the sound environment. I couldn't sleep. I couldn't escape. My acute sense of hearing became a curse rather than a blessing.

A Brief Musical Encounter

I recalled hearing a few minutes of music towards the end of my stay on the high dependency unit (HDU) after leaving the ICU. This provided the initial stimulus for the ICU-hear project. After leaving hospital I wrote:

> *"I recall trying to hold a TV remote in my hands on the high dependency unit and struggling to press the buttons. I couldn't follow TV programmes—the noise was upsetting. My husband turned it on at one point and there was some choral singing. It was wonderful—my only happy moment of that whole hospital stay. The music, the singing—it brought me back into the present moment temporarily. The music gave me both hope and comfort. The noise throughout my hospital stay had been a source of stress—so to hear some lovely music was a small but memorable bit of therapy".*

After my second hospital discharge (following an emergency re-admission), I sent a message to the Chair of the volunteer committee for Music in Hospitals™ North (who had previously worked as an ICU sister for 20 years), a charity I had volunteered with for many years. In it I wrote:

> *"There was a cheery moment right in the middle of the most serious low point. It [the music] transformed a horrible situation for me into one where I was instantly brought back to my former inner self".*

Effects of a Musical Awakening

The beauty and quality of the soothing music were a welcome respite, providing an awakening from the state of passive consciousness and displacement I had endured for numerous days and nights. I experienced feeling alert, focused and connected to the world again. Apathy, isolation and discomfort were forgotten. My mind cleared; I felt calm and organised. I was engaged and energised by lovely sounds. It transformed a disorientating, frightening experience, and that memorable impact stayed with me.

I subsequently wondered if that impact could have been even greater if I'd experienced music earlier—before being moved off the ICU and on to the HDU. Having volunteered with Music in Hospitals™ for several years I also wondered about the potential impact of receiving live music that was personalised and delivered under clinical supervision, where the music evolves to match the patient's condition.

Shared Patient Experiences

I wasn't aware initially that my personal experience resonated with many former ICU patients. After meeting others and sharing accounts of the ongoing effects following harrowing experiences of prolonged anxiety and delirium on the ICU, I realised the long-term ramifications an ICU stay can have. Despite immense gratitude for the devoted staff who ensured their survival, many former ICU patients struggled with daily life after discharge. Awareness of this fact is sometimes poor amongst friends, families, some GPs and many employers. Recovering pre-illness life and/or livelihood can be enormously challenging.

Practicalities of Launching ICU-Hear

When I met Sister Natalie Mason, critical care follow up lead at MRI ICU, at a regional patient support group, I spoke about my own patient experiences of intrusive noise, the impact of hearing music and my volunteering work with Music in Hospitals™. Natalie described a specific project addressing noise levels at night at the MRI. She had also researched the potential merits of live music. After talking together about the benefits that live music might provide for

patients and realising that we both were keen for it to happen, a pilot project was discussed with Music in Hospitals™. The ICU-hear project was subsequently pioneered at the MRI.

The aim of the pilot project was to make the critical care unit less clinical, altering the ambience by using soothing music. The staff recognise, understand and appreciate that the ICU can be a daunting experience. Care is taken to ensure that patients and/or relatives give permission for music to be played to them. Musicians ensure they are never in the way; they sensitively step aside should a patient need urgent medical attention. Staff have not been distracted by the musicians, and have welcomed the calming ambience on the unit that has been introduced by the music.

Selecting the Right Professional Musicians

It was paramount that the musicians selected for this work were sensitive, skilled, experienced professionals who could individualise delivery of live music at the bedside according to the changing needs of patients, families and the critical care staff. The musicians must be sensitive, empathetic and able to provide a gentle musical repertoire. They must be well versed in intensive care protocol, in addition to having a gentle, approachable personality and the resilience to adapt to any difficult situations they may witness. Music in Hospitals™ supports musicians with this and provides continuing professional development to enable the identification and development of effective common working practices.

The Importance of Live Music

Live performance (in contrast to recorded music) enables the musicians to observe and monitor any small changes in the patient, so that they may alter the tone and pace of the music accordingly.

The instruments played during the pilot study were chosen for their suitability for the environment and noisy bedside machinery—providing sounds that were engaging yet unobtrusive in this noise-polluted space. It is only more recently that I realised Florence Nightingale had recommended the beneficial healing effects of stringed instruments, the human voice and wind instruments, which she believed were "capable of having a continuous sound" (Nightingale 1860). These are precisely the instruments we have used so far for this work.

Music at the Hospital Bedside

Florence Nightingale introduced music as a beneficial nursing intervention for wounded soldiers during the Crimean War. Music in Hospitals™ started its work after World War Two, when it began playing live music to wounded servicemen in military hospitals. The charity maintains strong links with veterans in its work today. Some problems encountered by veterans, including PTSD, are also complications some ICU patients experience. Music in Hospitals™ has worked across the entire healthcare spectrum for decades, yet live music has rarely been requested for adult ICUs in the UK. After first playing in military hospitals 70 years ago, the charity's specialist musicians are once again playing live at the bedsides of seriously ill patients.

Next Phase

The multidisciplinary team involved throughout this venture has reviewed existing research studies alongside the pilot project outcomes. This is informing the next work phase, enabling consideration of targeted ways to introduce music as a non-pharmacological intervention. Insights gained over two years—before, during and after the pilot project—have provided an evidence base of data for further research. Whilst live music is utilised on neonatal ICUs, there is limited research on a sufficiently large scale involving live (rather than recorded) music on adult ICUs. It is recognised that music is a safe, relatively inexpensive intervention, and there is a pool of published research supporting the impact of music on health and body physiology (Harris 2014). One recent study concluded that live harp music in a critical care unit reduced pain by 27% (Chaisson et al. 2013). Another study found that listening to music improved patients' tolerance of mechanical ventilation. They also experienced less anxiety and required less sedation (Chan et al. 2013). Sedation in mechanically ventilated patients is a contributing factor to the onset of delirium (Ely 2004). Live music in neonatal ICUs is associated with infants' reduced heart rates and deeper sleep, potentially reducing time needed in hospital (Arnon et al. 2006).

There is clearly a place for live musical intervention in the care of critically ill people. Using live music for the alleviation of several aspects of the patient ICU experience may improve patient outcomes both on the ICU and also after discharge. The music can also potentially change the way relatives, staff and patients interact, making it easier to care for patients if patients and relatives are more relaxed.

Research design and preparation for furthering this project is at an advanced stage, and the pioneering work at MRI continues on a regular basis. Sid Richards, regional director for Music in Hospitals North, confirmed that following phenomenal feedback from patients, relatives and staff, more musicians are being carefully selected and trained for the ICU environment and the charity is working hard to expand the work across more UK hospitals to benefit ICU patients. ■

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Embracing Safety as a Science

We Need to Tell New Stories

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Since the publication of To Err is Human how do you rate progress in patient safety? What still needs to be done?

There's been some real progress, but the biggest indictment is that we don't know how much progress we've made, because we don't have a valid measurement system for harm. That's tragic and preventable, and we need to address it. We know the main reasons people die from preventable harm, and we have measures for some, like infections, but for most we don't. We should be able to say with confidence whether care is safer or not.

More clinicians and administrators are focusing on safety, but much of what we are training in is superficial and siloed. We have not embraced safety as a science like aviation and the oil and gas industries did. We borrowed error reporting from aviation, but in aviation they report mistakes and focus on sector-wide root cause analysis and risk reduction. We took team training from aviation, but we haven't mandated it or built it in to accreditation. Pilots cannot be certified if they don't pass the teamwork test, but there is no specialty that requires a teamwork test for medicine—you can be a horrible team player and be fully certified as a doctor. In healthcare we know we have harms from the designs of electronic medical records (EMRs) and medical devices, but we have not done sector-wide improvement efforts.

Stories are the most powerful force for change, because they define how you act in the world. The story that is guiding safety now is extrinsic motivation rather than intrinsic; hospitals and doctors have their pay docked to make them care more and there is very little evidence that it works.

The three new stories that I would love to see us tell are:

1) Harm is preventable rather than inevitable.

In our central line-associated bloodstream infection (CLABSI) work (Pronovost et al. 2006) we found that the 'secret sauce' wasn't the checklist, it was changing the belief systems. When we interviewed doctors and nurses and saw what changed when we spoke to them you could see in their eyes what they believed in their heart. They used to say that infections are inevitable. Now they say infections are preventable and they can do something about it.

2) Safety is a performance management system rather than a series of individual projects.

In healthcare systems quality and safety efforts are like whack-a-mole: they are working on a thousand different things, but with no integrating theory or framework. That is not how safe high-reliability organisations operate. Ultra-safe organisations integrate their work into an operating management system that includes governance and leadership, technology, training and recruitment as a seamless whole to eliminate all harm. Healthcare hasn't matured to that extent yet, although the Armstrong Institute for Patient Safety and Quality at Johns Hopkins Medicine is putting that systematic approach in. Early results are encouraging. For example, when looking at harms we saw that some nurses just out of orientation and residents coming out of training weren't skilled in the knowledge to prevent specific harms. This was predictable, because the people who run nurse orientation and residency programmes are completely separate from the people who run safety. So we presented them with the top ten reasons people suffer harm—it's a pretty clear list, and asked them to make sure that when people come out of orientation they have the skills to prevent those harms. We broke those silos down to focus on harm reduction. When you see safety as an integrated system all kinds of possibilities open up.

3) Safety is based on the design of safe systems rather than the heroism of clinicians.

Our clinicians spend over half their time documenting in the medical record—it adds no value. Our nurses spend about 20% of their time manually double checking medication changes to make sure the computer matches the infusion pump, when there is an electronic signal in both devices that in any other industry would do an electronic double

check. We made a checklist for CLABSI, but patients are at risk for a dozen harms. Every harm has a checklist with 5-10 items, and every item may need to be done 3-4 times a day. Multiply that and I am expected as a clinician to do 150 things every day. There is not a single EMR on the market that gives you any visual display if you have done them. It takes literally hundred of clicks and calculations to tell if you have done these things. Our goal is that within five years the inside of an ICU or a hospital ought to be as seamless as the inside of a cockpit. We are taking a disciplined systems engineering approach to plan the ICU of the future (Johns Hopkins Medicine 2016).

Johns Hopkins and Massachusetts General Hospital have successfully trialled peer-to-peer assessments in quality and safety (Mort et al. 2016; Pronovost 2017). Would you like to see this adopted more widely?

We have relied a lot on regulators to solve healthcare problems. Regulators are important, but they won't give the kind of healthcare we deserve. The reason is they can sanction us, and this creates a culture of judging not learning. I am fortunate to serve on the advisory board of the World Association of Nuclear Operators (WANO). After the Three Mile Island nuclear accident the nuclear company CEOs got together and said if there is another nuclear accident the public isn't going to trust nuclear power; we need to solve this ourselves. The regulators, though important, aren't going to fix this and in our own organisations we aren't strict enough, don't hold ourselves accountable or share best practices. They set up WANO, which does peer-to-peer review: one nuclear organisation goes and visits another and they use standard validated tools. It includes people from WANO and some who work in the individual nuclear facility. They have no sanctioning ability and the reports are confidential. They are ruthlessly honest, and it's in the spirit of improvement. We need this in healthcare, because when the regulators come we hide our mistakes rather than make them visible. We experimented with this and went into hospitals with near zero ICU infections and also higher infections to see if there is anything different (Pronovost and Holzmueller 2017). Every time we did this the CEOs and staff said this was the most potent quality improvement intervention, because they could be honest and make themselves vulnerable as they knew they were not going to be punished and would learn. If we see great things we share this so hospitals get credit for this and can focus on improvement. I would love to see healthcare have a global version of WANO with global peer-to-peer reviews. We would accelerate learning and improvement far quicker than we do from our current regulatory approach.

> **"Our goal is that within five years the inside of an ICU be as seamless as the inside of a cockpit"**

The Armstrong Institute's project EMERGE has developed a clinician app and a patients and family app. Are they in use now?

EMERGE is part of the integrated ICU project (**hopkinsmedicine.org/armstrong_institute/improvement_projects/project_emerge.html**). Clinicians can look at one screen with a picture of every ICU patient. If I am missing any one of those 150 things that needs to be done for a patient there is a red check next to their name. It is much more efficient. We are pilot testing it at Johns Hopkins and at UCSF, and we are looking to spread it. One of the main worries of patients is if they are going to be able to participate in decisions, to be informed and updated and have good communication. We let patients down on that, because we are working with clunky and clumsy technology and we are really busy. This app seems to be greatly aiding us to improve.

You have written that loss of respect and dignity is actually a patient harm. How can that be addressed?

With the new narrative that safety is not one project but an integrated operating management system it means we have to stop working on one harm at a time but on all harm. When we looked at how we defined harm, we realised we defined it too narrowly. For example, at Johns Hopkins, we now integrate patient experience, value and healthcare equity under quality and safety. Many of the complaint letters were not about technical care, but about lack of caring or respect. We decided to call disrespectful care a harm, because for the patient it is. When you ask patients what they care about, being respected is really important to them. We are working on a number of things: one is a simple measure of patients' perceptions of respect. A staff member asks patients if they feel respected and how well they were respected. In real time we could have a gauge of how patients are feeling, just as for temperature or blood pressure. The tablet that we developed for the patient-centred app is geared around what we found in focus groups that drives disrespect. Patients want you to know their names, they want to know the role of the care teams, they want information and they want you not to lose their stuff they come into the hospital with. The app is designed to help facilitate providing respectful care.

What is the smart list idea behind Doctella?

We learned that with disciplined improvement science, we can significantly reduce harm such as CLABSI. A key lesson was to be very clear about the behaviours people need to do, i.e. the checklist items. They need to be flexible for their local context. There's not one CLABSI checklist, but thousands in different hospitals. They are 90% similiar, but the 10% difference is what makes it work in the local context. Yet our CLABSI work used paper checklists. Doctella (**doctella.com**) is a platform to make checklists for all types of procedures, to make it easy for physicians to customise their own, engage patients in using them and provide analytics to monitor performance. Without having smart lists, we can't configure patient education material to engage patients in their care and share decision making. That's where the biggest impact is on patient outcome. When a patient has a procedure, their doctor can customise the checklist items to say, for example, to stop taking aspirin at this date or take this medication in the morning, and through secure text communicate with them and get feedback

on their compliance. We've seen about a 60% reduction in cancelled operating cases when patients use this because so much of this is due to miscommunication, with the patient saying, "I didn't know you wanted me to do this" or "I didn't know I was supposed to do that." We are early on in experimentation with this, but see great potential to have this smart list technology as a platform to connect patients and clinicians.

What are your hopes and expectations for personalised medicine in the future, particularly in critical care?

Personalised medicine has still much promise but also some hurdles to overcome if it is to benefit patients. In really safe organisations they don't just solve puzzles, they solve problems by integrating applied and basic research. Too often personalised medicine is viewed as only sequencing genes without making patients benefit from it. This is played out in how some people use the term learning health system, largely researchers, who are learning and thinking about adding new knowledge. But those of us who have operational responsibility for quality and safety, our thinking is about high-reliability organisations and eliminating harm and those two ideas need to be combined. In my view personalised medicine has such great hope, but it is only going to be realised if it is combined with applied research and healthcare managers where genomics, proteomics, environmental-omics or epigenetics are just another variable in a risk model to help patients thrive and stay well. If we don't apply what we learn I think we are going to spend a lot of money and not have a whole lot to show for it. The difference between what we are doing in safety and quality with applied research and precision medicine is that applied researchers start at the end and work backwards. We start with the goal of eliminating harm, continuously improving patient outcomes and experience and eliminating waste in healthcare, then work backwards to design a system that does that.

> "see precision or personalised medicine as another input to make sure we optimise patient experience"

Applied research and precision medicine is feed forward, it asks is A better than B, is this gene related to this disease or not. That is important, but we need to combine both modes of thinking, because if you just ask if A is better than B, we have a whole lot of experience for decades that shows much of that knowledge never reaches patients. We know a lot of therapies that work that patients don't get. So the idea is to see precision or personalised medicine as another input to make sure we optimise patient experience. Perhaps the checklist for you differs from the checklist for me, because of your genes and I need to make a checklist that does that. We have to be mindful of precision medicine offering the hope of giving patients the right therapies. We know that many cancers are not one disease but ten different diseases and each may need a different therapy or dose of drug because you metabolise differently. This is humbling, because now we have to rely on memory to understand all those ten permutations and what each of those therapies should be. When every patient is at risk of a dozen harms there are 150 things we need to do, and if you add personalised medicine it may mean that I need to be aware of a thousand different things to do. We far exceed the cognitive ability of our brains. We have to partner with system engineers and computer scientists to make sure that patients realise the benefit of precision medicine. If we rely solely on our memory, patients will suffer harm and it may even increase, because we are adding such complexity to the system. Ultimately to realise benefits to patients, healthcare will need to think like an engineer, solving problems, and like a biomedical researcher solving puzzles. This is what Bell Labs did. This is what we are trying to do at the Armstrong Institute. ■

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Intensive Care in China

Medicine in mainland China has progressed rapidly during the past 20 years along with rapid economic development. Although the number of ICU beds, doctors and nurses has increased, postgraduate professional education is still lacking. This article gives an overview of the history and current state of intensive care in China.

Critical care was recognised as a medical speciality in China less than 10 years ago. However, the development of intensive care began in the 1980s when the first intensive care unit (ICU) with a single bed was opened in 1982 at Peking Union Medical College Hospital, which opened the first department of critical care medicine in 1984 with a seven-bed ICU, chaired by Professor Dechang Chen, who is recognised as the father of critical care in China (Qiu et al. 2001; Wang and Ma 2006). **Figure 1** is a timeline of the main developments.

Intensive Care Infrastructure

A 1989 Ministry of Health regulation that made it mandatory for hospitals to have an ICU in order to be accredited as a tertiary hospital led to rapid growth (Qiu et al. 2001; Wang and Ma 2006). Currently there is no census information on the number of intensive care beds in China. An estimate from 2010 put the number of beds as approximately 51,891 or 1.8% of hospital beds, corresponding to 3.91 ICU beds per 100,000 population (Du et al. 2010). The estimated number of ICU physicians is between 33,210 and 49,815 and ICU nurses between 71,091 and 104,820 (Du et al. 2010). Hospital and ICU provision varies greatly across the country. **Figures 2-4** and **Table 1** show hospital bed and healthcare staff provision in Beijing and across China compared to other countries.

Professional Societies

Before intensive care medicine was recognised as a specialty, the speciality societies involved in critical care (surgery, anaesthesiology, emergency medicine and pulmonology) had critical care sections (Du et al. 2010).

There are now three professional societies for critical care, which collaborate closely. The Chinese Society of Critical Care Medicine (CSCCM) was established in 1997, and has roughly 700 members. It promotes critical care medicine, and liaises with government bodies, and with international critical care societies, including the World Federation of Societies

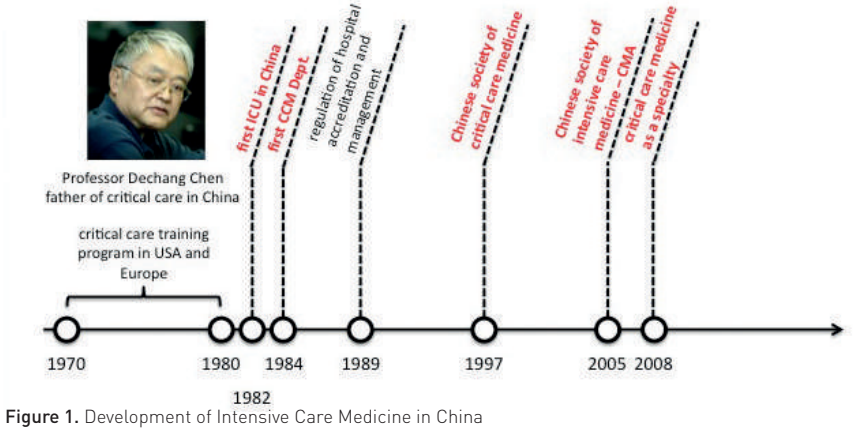

Figure 1. Development of Intensive Care Medicine in China

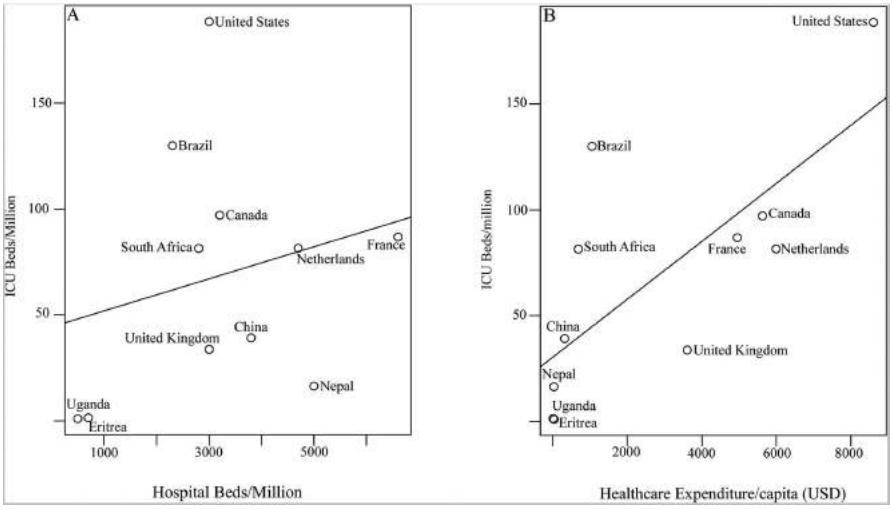

Figure 2. Comparison of the relationship between ICU beds and hospital beds (panel a), and between ICU beds and national healthcare expenditure per capita (panel b) in low versus selected high-income countries.

Source: Murthy et al. (2015) Reproduced under CC BY 4.0 (creativecommons.org/licenses/by/4.0)

Table 1. Critical Care Resources in Beijing, 2014

Population	21,516,000 (incl. 8,187,000 immigrants)
Hospitals	672
Hospital beds	109,789
ICU beds	2,878 (2.6%) (in 192 ICUs)
Physicians	89,590
ICU physicians	1,365 (1.5%)
RNs	106,167
ICU nurses	4,818 (4.5%)

Sources: bjstats.gov.cn/tjsj/tjgb/ndgb/201511/t20151124_327764.html [Accessed: 6 February 2017]; http://xxzx.bjchfp.gov.cn/tonjixinxi/weishengtongjijianbian/2014nianjianbian/qsylwszyqk html [Accessed: 6 February 2017]

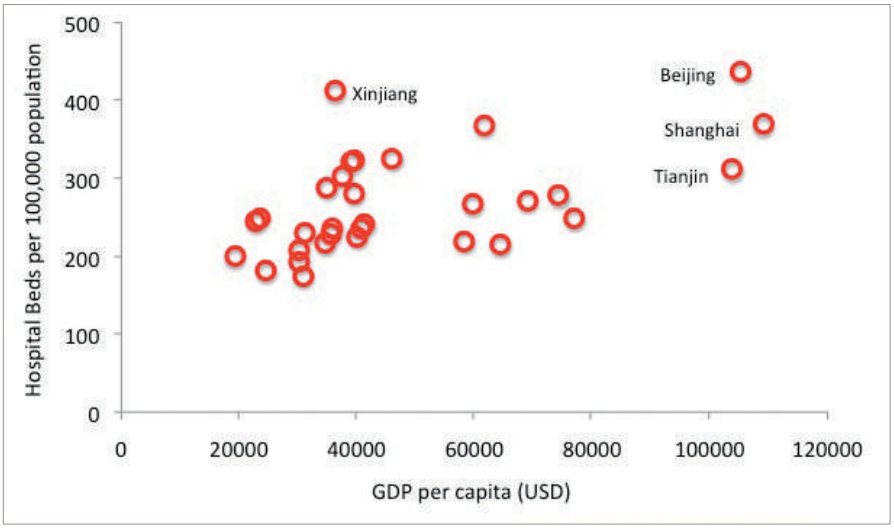

Figure 3. Geographic Variation in Health Resources (Hospital Beds per 100,000 population)

Source: National Bureau of Statistics of China. China Statistical Yearbook 2014. [Accessed: 1 March 2015] Available from stats.gov.cn/tjsj/ndsj/2014/indexch.htm

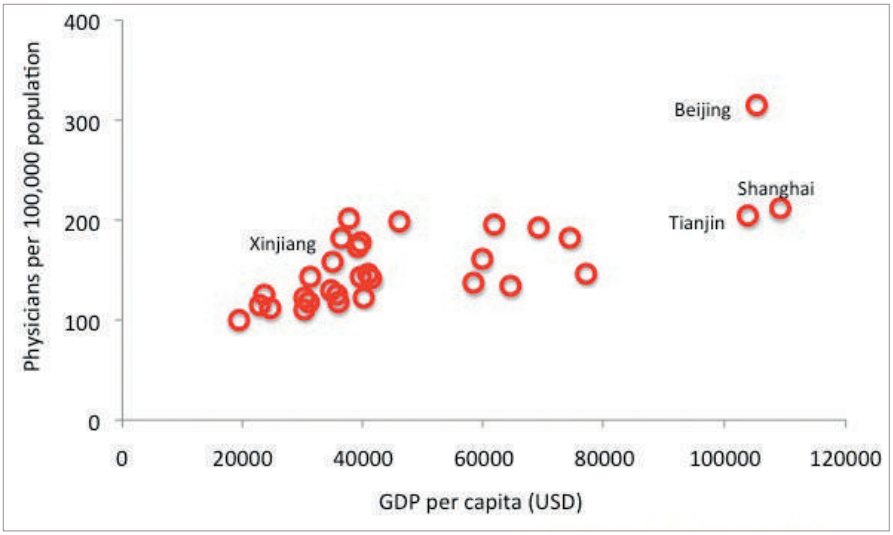

Figure 4. Geographic Variation in Health Resources (Physicians per 100,000 population)

Source: National Bureau of Statistics of China. China Statistical Yearbook 2014. [Accessed: 1 March 2015] Available from stats.gov.cn/tjsj/ndsj/2014/indexch.htm

of Intensive and Critical Care Medicine, the Asia Pacific Association of Critical Medicine and the Global Sepsis Alliance. It organises a national conference every year. The last conference in 2016 was attended by more than 3000 delegates. The Chinese Society of Intensive Care Medicine was established under the umbrella of the Chinese Medical Association in 2005. The CSICM has developed clinical practice guidelines on sepsis management, mechanical ventilation and nutritional support. The professional certification of intensivists is undertaken by the Chinese Association of Critical Care Physicians (CACCP), which was founded in 2009 and is affiliated to the China Medical Doctors Association.

Education and Training

Pathways to the intensive care medicine specialty follow 3-4 years of fellowship training in internal medicine, anaesthesia, emergency medicine or general surgery (Du et al. 2010). The recognition of critical care medicine as a specialty in 2009 was in part a recognition of intensivists' response to healthcare pandemics and emergencies, such as SARS and the Wenchuan earthquake in 2008 (Du et al. 2010). As yet, there is no formal accredited training programme in intensive care medicine. A pulmonary and critical care medicine fellowship training programme has been established by a collaboration between the Chinese Thoracic Society and the American College of Chest Physicians (Qiao et al. 2016), as one of four pilot subspecialities to be recognised by the government. It is hoped that a multidisiciplinary approach to subspecialty training will be adopted going forward (Du and Weng 2014). To that end the China Critical Care Clinical Trials Group (CCCCTG) and the Task Force of Core Competencies in Intensive and Critical Care Medicine Training in China have developed a list of 129 core competencies which will assist in developing training programmes (Hu et al. 2016).

The professional societies provide continuing medical education and training. The Chinese Society of Critical Care Medicine provides the Basic Assessment and Support in Intensive Care (BASIC) course, Improve Proficiency in Ventilation (IMPROVE), Fundamental Critical Care Support and Fundamental Disaster Management courses. The Chinese Society of Intensive Care

Medicine offers the Chinese Critical Care Certificate Course. Other educational programmes are offered with international partners: for example, the Multiprofessional Critical Care Review Course (MCCRC) with the Society of Critical Care Medicine.

China Critical Care Clinical Trials Group

The China Critical Care Clinical Trials Group (CCCCTG) was established in 2009. The group includes 25 tertiary hospitals (21 of which are teaching hospitals) in 21 provinces. The hospitals include 19 general, 4 surgical and 2 medical ICUs (**Tables 2-4**). The group has completed 12 studies, with 3 ongoing and 2 in the planning. It has 15 papers and 1 book chapter published. It also participates in InFACT, the International Forum for Acute Care Trialists, and in the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).

One of the first studies published by the CCCCTG was an analysis of the adult patient population that stayed in any of 22 participating ICUs for ≥ 24 hours from July 1 to August 31, 2009 (**Figures 5-6**) (Du et al. 2013).

Critical Care Research

Chinese researchers are increasingly publishing in the 7 major critical care journals (Ma and Du 2013). While the number of articles in critical care journals is increasing (Li et al. 2010), average citations fell in the years up to 2008 (Li et al. 2010). Several obstacles to critical care research still exist in China (Ma and Du 2013):

- **Lack of training in clinical research:** this results in poor study design, inadequate description of the methods, suboptimal reporting of the results, and getting carried away in the discussion
- **Inadequate resources:** inadequate funding, unavailability of research nurses and/or biostatisticians
- **Language barrier:** poor writing, not following the manuscript preparation instructions

China is increasingly participating in international studies (**Table 6**). Registration of clinical trials is increasing (from 1,945 registered in 2013 (Ma and Du 2013) to 9,058 for mainland China and 1,298 for Hong Kong

Table 2. Participating ICU information in 2009

	Total	Mean ± SD	Median (IQR)	Range
ICU beds	499	22.0 ± 14.3 (1.2 ± 0.5%)	18 (12 to 28)	8 to 76
ICU physicians	317	13.2 ± 10.6	12 (8 to 13)	6 to 60
ICU nurses	1,010	42.1 ± 32.1	33 (26 to 45)	15 to 175
Admissions	25,872	1,078 ± 945	791 (438 to 1,293)	81 to 3,907
Mechanical ventilation	16,091	700 ± 660 (66.8 ± 24.4%)	434 (271 to 886)	27 to 2,605
CRRT	2,848	124 ± 161 (13.3 ± 12.4%)	55 (37 to 119)	0 to 580
Death	2,863	119 ± 111 (14.4 ± 11.7%)	92 (45 to 145)	8 to 462

Table 3. Critical Care Resource: 2009 to 2014

	2009	2010	2011	2012	2013	2014
ICU beds	527 22.0 ± 14.3 8 – 76	736 30.7 ± 29.9 6 – 130	800 33.3 ± 33.6 8 – 152	892 37.2 ± 35.3 8 – 152	764 30.6 ± 28.1 8 – 152	826 33.0 ± 31.6 8 – 172
ICU physicians	317 13.2 ± 10.6 6 – 60	293 13.3 ± 4.7 4 – 24	381 15.9 ± 7.7 4 – 44	418 17.4 ± 8.7 3 – 48	418.5 16.7 ± 6.9 2.5 – 28	444 17.8 ± 7.4 6 – 31
ICU nurses	1,010 42.1 ± 32.1 15 – 175	1,585 68.9 ± 61.8 20 – 296	1,778 77.3 ± 77.0 22 – 380	2,061 89.6 ± 94.6 22 – 436	1,885 75.4 ± 69.5 16 – 382	2,042 81.7 ± 77.3 25 – 428

Table 4. Patients in Participating ICUs: 2007 to 2014

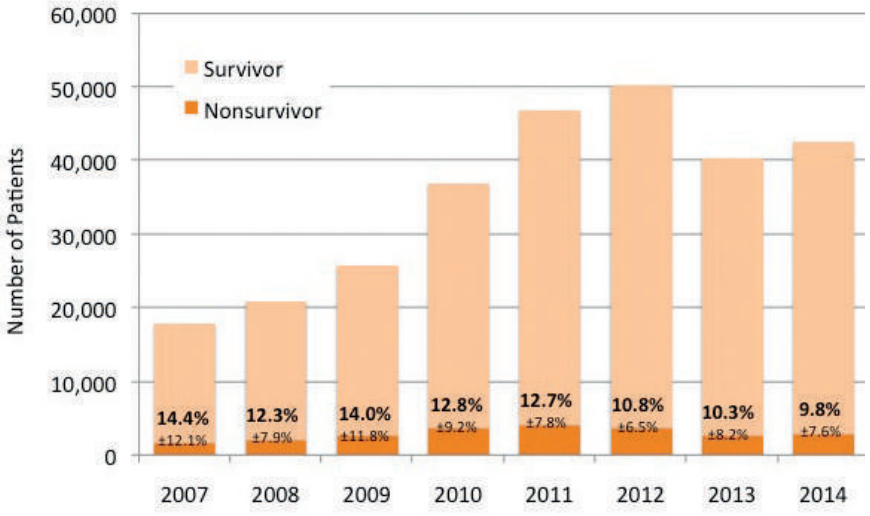

Table 5. Patients in Participating ICUs: 2007 to 2014

	2007	2008	2009	2010	2011	2012	2013	2014
Ventilation	10,685 65.9±22.6%	12,649 66.5±23.5%	16,090 66.8±24.4%	21,366 59.8±24.4%	28,873 61.2±25.0%	28,087 55.8±26.1%	28,285 66.2±23.2%	29,818 66.9±23.5%
PiCCO	124 5.2±8.9%	183 1.5±3.2%	526 2.8±4.8%	288 1.5±2.2%	588 3.1±5.5%	849 3.7±5.7%	733 2.9±3.6%	822 3.4±4.3%
PAC	139 5.8±6.9%	95 1.0±1.7%	93 0.8±1.7%	87 0.8±2.0%	109 0.8±2.0%	98 0.7±1.9%	41 0.3±1.0%	71 0.5±2.1%
CRRT	1,364 12.2±12.3%	1,820 12.2±10.8%	2,848 13.3±12.4%	2,793 10.3±7.7%	3,755 10.3±7.7%	4,482 11.8±8.3%	3,480 11.1±7.6%	4,185 12.6±8.8%

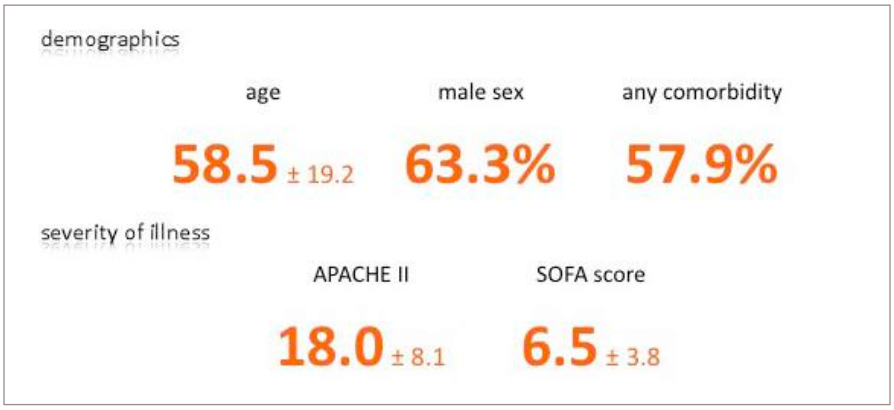

Figure 5.

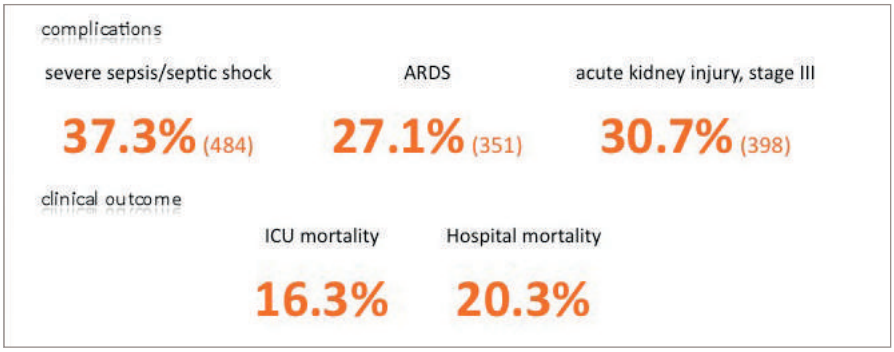

Figure 6.

Table 6. International Collaborations

Study	No. ICUs All	No. Pts All	No. ICUs China	No. Pts China
BEST Kidney (2000-2001)	54	1,738	2 (3.7)	77 (4.4)
EPIC II (2007)	1,265	13,796	13 (1.0)	
SAFE-TRIPS (2007)	391	1,955	57 (14.6)	503 (25.7)
Nutritional Support Survey (2007)	158	2,946	21 (13.3)	370 (12.6)
EUROBACT (2009)	162	1,156	10 (6.2)	59 (5.1)
MOSAICS (2009)	150	1,285	40 (26.7)	189 (9.1)
3rd Mechanical Ventilation Survey (2010)	927	4,151	43 (4.6)	571 (13.8)
ICON Study (2012)	730	10,069	?	?

registered at clinicaltrials.gov at the time of writing (clinicaltrials.gov/ct2/search/map/click?map.x=597&map.y=169), of which 3369 were open. The National Natural Science Foundation of China (NSFC) began accepting grant applications for critical care research in 2010.

Conclusion

Clinical practice is similar to western countries, but critical care resources are at the lower end. Professional training/accreditation and more participation in research is needed. ■

Conflict of Interest

Bin Du declares that he has no conflict of interest.

Directory

Chinese Society of Critical Care Medicine csccm.org/cn

Statistics	
Total population (2015)	1,400,000,000
Gross national income per capita (PPP international $, 2013)	11
Life expectancy at birth m/f (years, 2015)	75/78
Probability of dying between 15 and 60 years m/f (per 1 000 population, 2013)	103/76
Total expenditure on health per capita (Intl $, 2014)	731
Total expenditure on health as % of GDP (2014)	5.5

Source: World Health Organization who.int/countries/lka/en
Statistics are for 2013

For full references, please email editorial@icumanagement.org or visit https://iii.hm/8x4

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10-12 Smart Meeting Anesthesia Resuscitation Intensive Care
Milan, Italy
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11-13 2nd Annual Dubai International Conference on Infectious Diseases and Vaccination
Dubai, UAE
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14-17 Future of Critical Care - A Brainstorming Meeting
Lisbon, Portugal
https://iii.hm/8wr

18-20 2nd European Pediatric Resuscitation and Emergency Medicine Conference, Gent, Belgium
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30-31 Metabolic and Nutritional Issues in the ICU
Brussels, Belgium
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3-5 Euroanaesthesia 2017
Geneva, Switzerland
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8-9 Neurosciences in Intensive Care International Symposium
Paris, France
https://iii.hm/6ph

13-14 BRACE (Brain Critical Care & Emergencies) Meeting
Brussels, Belgium
https://iii.hm/6vq

15-17 World Congress of the Abdominal Compartment Society
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ICU MANAGEMENT AND PRACTICE IS PUBLISHED BY
MindBYTE Communications Ltd
9, Vassili Michailidi CY-3026 Limassol, Cyprus
E-mail: office@icu-management.org
Website: icu-management.org

PUBLISHER
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One year 55 Euros + 5% VAT if applicable
Two years 90 Euros + 5% VAT if applicable

Note: Participants of the International Symposium on Intensive Care and Emergency Medicine receive a one year subscription as part of their symposium fee. Prices without VAT.

PRODUCTION, PRINTING AND DISTRIBUTION
Gyomai Kner Nyomda Zrt, Hungary
Total classic and digital distribution: 21,500
ISSN = 1377-7564

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