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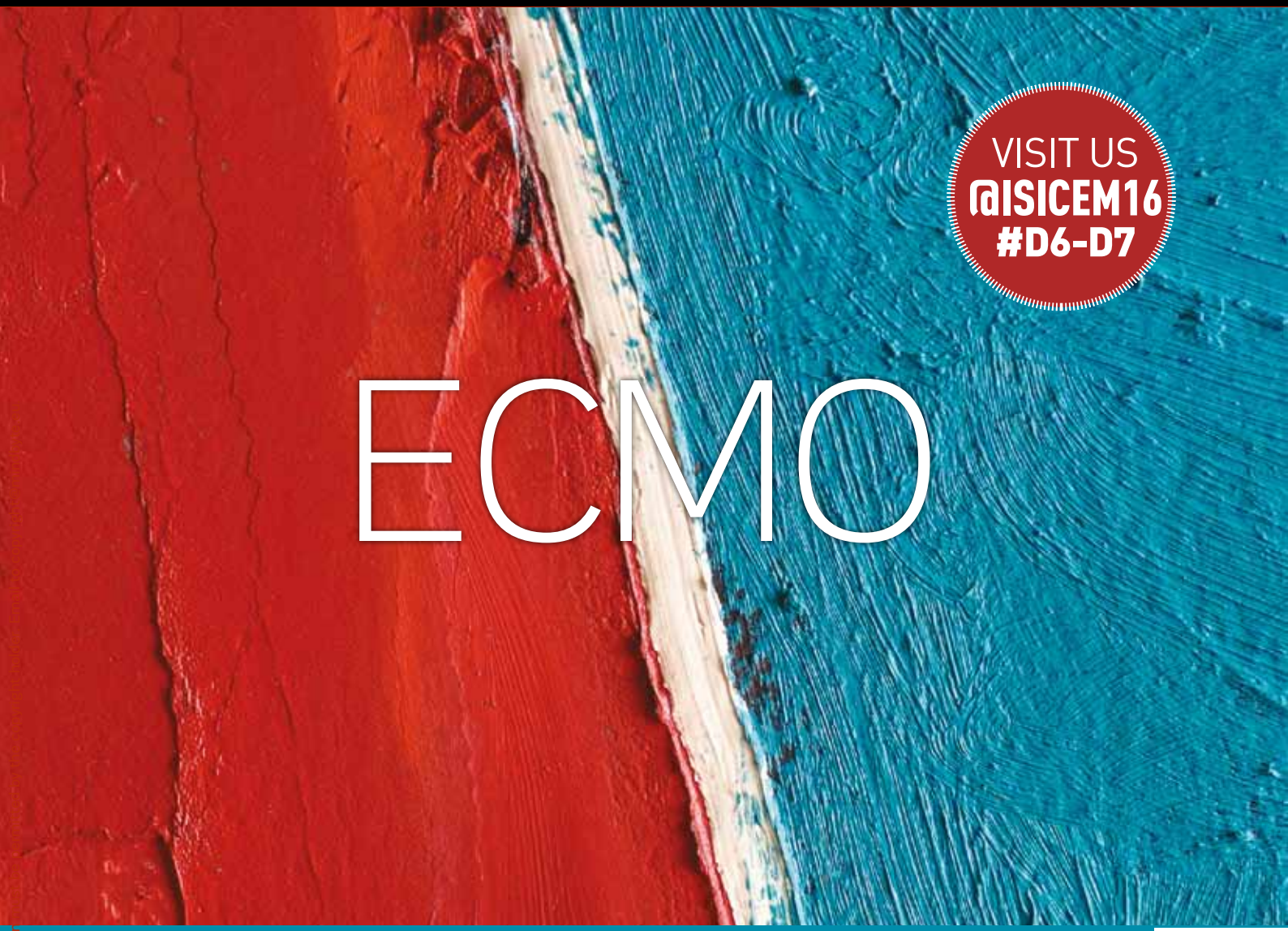

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EXTRACORPOREAL MEMBRANE OXYGENATION

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The use of extracorporeal membrane oxygenation (ECMO) in critical care is growing. From its initial use back in the 1950s in cardiac surgery, it is now an important tool for life-saving organ support, with clear indications for use in neonates and growing use in paediatric ICUs. ECMO for adult patients is also expanding in use (over 400% between 2006 and 2011 in the USA, for example (Sauer et al. 2015)). In our cover story we hear about ECMO in immunocompromised patients, its use with trauma patients, and the role of the perfusionist in European ECMO centres.

First, Matthieu Schmidt and Alain Combes consider the use of ECMO in immunocompromised patients with acute respiratory distress syndrome (ARDS). It is controversial, as these patients are at greater risk of ECMO-related complications. However, pending evidence from large-scale trials, Schmidt and Combes recommend ECMO for severe cases in patients in whom there is prospect of a cure. Thomas Bein then explores why and when to use extracorporeal lung assist with trauma patients, despite the challenges that are immense even for a high-level trauma centre. Perfusionists perform a key role in the operating room (OR) during cardiac surgery. However, when the technology is used outside the OR, roles and responsibilities are varied. Leen Vercaemst reports on a survey by the European Extracorporeal Life Support Organization that explored the perfusionist role across Europe.

Our 2016 series is on Biomarkers. Pedro Póvoa, Jorge Salluh, Vandack Nobre and Ignacio Martin-Loeches review what is new in biomarker-guided antibiotic therapy and describe an algorithm for decision-making using time/clinic course and biomarker level.

The Matrix section starts with a look at medication safety. James Hanison and Tony Thomas outline strategies to reduce risks, with a caveat that technology is not necessarily the solution. Next, Caleb Fisher, Darshi Karalapillai, Daryl Jones and Rinaldo Bellomo review the tools available to diagnose frailty, its application to perioperative and critically ill patients and who can administer these tools. While patient frailty is an important factor in patient outcome, there is no consensus definition of "frailty" and the two main frailty models are validated for community use rather than at the bedside.

In the ongoing fight against hospital-acquired infection antimicrobial copper is increasingly recognised as a key tool. Angela Vessey explores the evidence and the cost benefits for replacing high touch surfaces such as bedrails and IV poles with equipment that includes copper alloys. Another potentially cost-saving tool in the ICU is bedside ultrasonography. Nidhi Nikhanj shares six proven steps from his organisation based on their introduction of point-of-care ultrasound in critical care. In the final article in the Matrix section, Sven Zenker starts from the observation that critical care has the highest density of quantitative data derived from direct physiological measurement. However, the tools to turn this measurement into understanding to drive better protocols are not yet routinely available. Zenker explores the reasons and suggests possible solutions.

In our Management section this year we will hear not only from intensivists, but from other members of the critical care team. We start appropriately in this issue with the patient at the centre. Catherine White, who is a critical care survivor working for the ICUsteps charity, explains why patients and families should be involved in ICU service planning and research and provides pointers for intensive care teams on the best way to promote involvement.

Next Ella Segaran explores the role of the dietitian in critical care, a role that is fundamental and looks set to grow even further, as advanced-level dietitians in the UK have just gained supplementary prescribing rights. Then Girendra Sadera and Victoria Treadway explain why a librarian on ward rounds can assist the critical care team as a 'knowledge mobiliser'. Last, Hans Flaatten looks at the vexed issue of bibliometrics and new methods of looking at publication impact in this age of social media.

My colleague Professor Todd Dorman is a long-standing member of the *ICU Management & Practice* Editorial Board. He just became President of the Society of Critical Care Medicine, and I am delighted that he could take time for an interview in this issue.

Our Country Focus is Denmark. Prof. Ingrid Egerod is an active critical care researcher, and she is interviewed about the state of critical care in Denmark. Last, Prof. Anders Perner writes about the recently-established Centre for Research in Intensive Care, a focal point for critical care researchers in Denmark.

This issue will be out at the International Symposium on Intensive Care and Emergency Medicine in Brussels. I hope to see you there!

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

Jean-Louis Vincent

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COVER STORY

SERIES - BIOMARKERS

MATRIX

POINT OF VIEW

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Presenters

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
President, World Federation of Intensive and Critical Care Societies (WFSICCM)

Fluid and Blood Management: Optimizing Titration and Administration Decisions

Maxime Cannesson, MD, PhD
Professor of Anesthesiology and Vice Chair for Perioperative Medicine
UCLA, Los Angeles, California, USA

Non-invasive Monitoring of Oxygen Delivery: New Frontiers

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SEPSIS-3 - TOWARDS EARLIER RECOGNITION AND MANAGEMENT

The updated definitions and clinical criteria for sepsis have been welcomed by Professor Jean-Louis Vincent, *ICU Management & Practice's* Editor-in-Chief, who says: "we are finally back to reason – the new recommendations fit the current language." The new definitions are published in the 23 February issue of *JAMA*, and aim to facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis as well as offer greater consistency for epidemiologic studies and clinical trials. Because no gold standard diagnostic test exists, the joint Society of Critical Care Medicine and European Society of Intensive Care Medicine task force sought definitions and supporting clinical criteria that were clear and fulfilled multiple domains of usefulness and validity.

The report of the Task Force is published along with two supporting reports that outline the evidence for the new definitions (Seymour et al. 2016; Shankar-Hari et al. 2016). Of note is the use of analyses in large cohorts to provide quantitative information in support of the revised criteria. The Task Force's review of the evidence found that previous definitions included an excessive focus on inflammation, that the continuum model was misleading and that severe sepsis is a redundant term. In addition the criteria for systemic inflammatory response syndrome (SIRS) lacked adequate specificity and sensitivity. Multiple definitions and terminologies are in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality.

The Task Force write: "Although qSOFA is less robust than a SOFA score of 2 or greater in the ICU, it does not require laboratory tests and can be assessed quickly and repeatedly. The task force suggests that qSOFA criteria be used to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken."

The updated definitions have been through a rigorous voting and consultation process, and are endorsed by 31 societies. The task force write that they want to encourage debate: "Aspects of the new definitions do indeed rely on expert opinion; further understanding of the biology of sepsis, the availability of new diagnostic approaches, and enhanced collection of data will fuel their continued reevaluation and revision."

They conclude: "Hopefully, the next iteration of this consensus process will take full advantage of the rapidly advancing understanding of molecular processes that lead from infection to organ failure and death so that sepsis and septic shock will no longer need to be defined as a syndrome but rather as a group of identifiable diseases, each characterised by specific cellular alterations and linked biomarkers. Such evolution will be required to truly transform care for the millions of patients worldwide who develop these life-threatening conditions."

In an accompanying editorial, Edward Abraham, MD, of the Wake Forest School of Medicine, Winston-Salem, NC, USA, writes that more information about the molecular and cellular characterisation of sepsis may have been helpful to assist with segmenting patients into subgroups based on underlying microbiology, pathophysiology or cellular alterations. He suggests that while the new definitions may help in facilitating early identification of patients with this condition, they will be of only limited help in directing specific therapies to individual patients or in designing clinical trials focused on specific mechanisms of sepsis-induced organ dysfunction. ■

Key Points from the Recommendations

- Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.
- In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA):
  - respiratory rate of 22/min or greater;
  - altered mentation (mental activity), or;
  - systolic blood pressure of 100 mm Hg or less.

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ARDS STILL UNDER-RECOGNISED, UNDER-TREATED


John Laffey (image credit: St. Michael's Hospital)

Acute respiratory distress syndrome (ARDS) seems to be under-recognised, under-treated and associated with a high risk of mortality, according to the results of the ESICM LUNG-SAFE observational study, published in *JAMA*. Speaking to *ICU Management & Practice*, John G. Laffey, MD, MA, of the Departments of Anesthesia and Critical Care Medicine, Keenan Research Centre for Biomedical Science, St Michael's Hospital, University of Toronto, Canada, said: "This global study gives us unparalleled insights into the burden and current management approaches for ARDS in the 21st century. We now need to understand and overcome barriers to clinician recognition of ARDS, and to continue to develop the evidence base for interventions that may benefit patients suffering from this devastating condition."

Laffey acknowledged that the true extent of ARDS came as somewhat of a surprise: "We had anticipated finding an incidence of ARDS of approximately half of what we actually found in the LUNG-SAFE study. We think that the difference is explained by the fact that we did not rely on clinician recognition of ARDS, but rather collected data directly on each of the Berlin diagnostic criteria, enabling us to make the diagnosis directly. This enabled us to determine that 10% of ICU admissions globally suffer from ARDS."

The Large Observational Study to UNderstand the Global Impact of Severe Acute Respiratory FailurE (LUNG-SAFE) study was initiated by the European Society of Intensive Care Medicine. The group studied patients undergoing invasive or noninvasive ventilation, on whom data was collected during 4 consecutive weeks in winter 2014 in 459 ICUs from 50 countries across 5 continents.

Results

The participating ICUs admitted 29,144 patients:

- 3,022 (10.4%) fulfilled ARDS criteria;
- 2,377 patients developed ARDS in the first 48 hours and received invasive mechanical ventilation;
- ARDS patients represented 23.4% of ventilated patients, ranging from 0.27-0.57 cases per ICU bed per 4 weeks across the different continents.

In-hospital mortality

- mild ARDS 34.9%
- moderate ARDS 40.3%
- severe ARDS 46.1%

Recognition

60.2% of ARDS cases were identified at any point during their clinical course; recognition ranged from 51.3% in mild to 78.5% in severe ARDS. Only 34% of cases were identified at the initial time that ARDS criteria were met. Clinician recognition of ARDS was associated with higher PEEP, greater use of neuromuscular blockade and prone positioning. Factors that prompted clinician recognition of ARDS were found to be younger patient age, lower predicted body weight, the presence of extrapulmonary sepsis or pancreatitis, and greater disease severity. Lower numbers of nurses and physicians per ICU patient were both associated with reduced clinician recognition of ARDS.

Treatment

Laffey explained that they found that over one third of patients did not receive protective lung ventilation strategies; this was defined as a tidal volume of up to 8ml/kg predicted body weight and a plateau pressure of 30 cmH_2O or less. Less than 2% of patients received the combination of high tidal volumes and had high plateau pressures. The use of adjunctive measures to aid gas exchange, such as prone positioning (used in 16.3% of patients with severe ARDS), the use of neuromuscular blockade, recruitment manoeuvres or extracorporeal support was also quite low. Laffey added: "This may be due in part to doubts in regard to the strength of the evidence for these adjunctive approaches. This can be addressed by performing additional definitive studies into these interventions."

Next Steps

In an accompanying editorial, Brendan J. Clark, MD and Marc Moss, MD, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine, Aurora, USA, note that the under-recognition of ARDS is concerning, especially when clinicians probably knew their hospital was participating in the LUNG-SAFE study and were subject to the Hawthorne effect. Clark and Moss write, "it is possible that…these low rates of clinician recognition of ARDS are overestimates of what likely happens in daily practice."

Despite good evidence on effective treatment of ARDS, bridging the evidence-practice gap remains difficult, acknowledge Clark and Moss. Multiple approaches may be needed, such as an improvement "champion", interprofessional teamwork, and at the macro level financial investment in implementation science. They conclude: "The medical and critical care community should prioritise the proper implementation of beneficial therapies, engage the necessary stakeholders, and take the next steps to dial in the evidence to improve the treatment and outcomes of patients with ARDS."

Laffey emphasised the need to find more reliable ways to diagnose ARDS. " We need to increase our efforts," he said. "ARDS remains a syndrome diagnosis, and therefore requires clinician recognition of a pattern of clinical findings to make the diagnosis. While the reasons underlying clinician failure to recognise ARDS in critically ill patients are complex, the fact that there is no single test for diagnosing ARDS is a likely contributing factor." ■

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EXTRACORPOREAL MEMBRANE OXYGENATION FOR IMMUNOCOMPROMISED PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

Improved Outcomes of Immunocompromised Patients Admitted to the ICU

Immunocompromised patients, who include patients with haematological malignancies (HMs), solid tumours, solid-organ transplants, human immunodeficiency virus (HIV) or long-term corticosteroid use, are increasingly admitted to intensive care units (ICUs). Their survival has improved markedly in recent years. For example, most patients with HMs and acute respiratory failure (62%) and/or shock (42%) require ICU admission. Hospital, and 90-day and 1-year post-ICU–admission survival rates were 61%, 52%, and 43%, respectively (Azoulay et al. 2013). Recently, among 1,004 patients with malignancies from mild (252, 25.1%), moderate (426, 42.4%) or severe (326, 32.5%) acute respiratory distress syndrome (ARDS), their respective mortality rates were 59%, 63% and 68.5% (p=0.06) (Azoulay et al. 2014). In addition, mortality of such populations declined from 89% in 1990–1995 to 52% in 2006–2011 ($p < 0.0001$). Similar trends were observed for human immunodeficiency virus (HIV)-infected patients admitted to ICUs in a 1999–2010 multicentre cohort study in France (Barbier et al. 2014). In that cohort, 39.8% of the patients were admitted for acute respiratory failure (ARF) and they increasingly received mechanical ventilation (rising from 42.9% to 54.0%) over the study period. Although ICU management of immunocompromised patients has improved for over a decade, their outcomes remain poorer than those of the general population of ARDS patients. However, the higher numbers of immunocompromised patients admitted to ICUs and their decreased ARDS-attributable mortality raise the question of whether to extend and generalise the use of extracorporeal membrane oxygenation (ECMO) to the immunocompromised (Azoulay et al. 2014). Notably, these patients are likely to develop specific ECMO-related complications more frequently and this possibility needs to be taken into account.

> “likely to develop specific ECMO-related complications more frequently”

Impact of Immunocompromised Patients’ Premorbid Conditions on ECMO-Related Complications

Immunocompromised patients are at risk for life-threatening acute illness as a result of infection, toxicity of intensive treatment and targeted therapies, and decompensation of comorbid conditions.

Bleeding

A bleeding complication is the first major risk for these patients on ECMO, especially for those with HMs. Indeed, the ECMO device’s non-biological surface, in the context of the patient’s underlying severe disease, results in massive inflammatory and clotting system activation. Consequently, anticoagulation exposes the patient to haemorrhagic complications, which are common during ECMO management. In a review of the ECMO-associated complications of 1,763 patients, 33% of them experienced severe bleeding (Zangrillo et al. 2013). Similarly, ECMO use during the A(H_1N_1) influenza pandemic was associated with 29% bleeding events (Davies et al. 2009). In a

recent report on ECMO use in a small cohort of patients with HMs, 11/14 patients were thrombocytopenic, with their median (IQR) platelet count at 35 (26–51) G/L (Wohlfarth et al. 2014). Although biocompatible latest-generation ECMO devices allow reduction of the anticoagulant dose, outcomes and overall costs are strongly impacted by haemorrhagic complications.

Nosocomial Infection

Nosocomial infection is the second major risk for immunocompromised patients on ECMO. Indeed, that risk on ECMO is already very high for patients without immunodeficiency, and obviously affects outcomes. Among 220 patients who received ECMO support for >48 hours, for a total of 2,942 ECMO-days, 142/220 (65%) developed nosocomial infections (Schmidt et al. 2012), with ventilator-associated pneumonia, bloodstream or cannula infections and mediastinitis occurring respectively in 55%, 18%, 10% and 11% of them. More critical status at ICU admission, which includes being immunocompromised, was associated with a subsequent risk of developing a hospital–acquired infection.

Data on Paediatric Populations

ECMO use to counter respiratory or cardiac failure in immunocompromised children has been limited (Di Nardo et al. 2014; Gow et al. 2009; Gow et al. 2006). Some authors have argued that patients with cancer or end-stage acquired immunodeficiency syndrome should be denied access to ECMO (Green et al. 1995; Masiakos et al. 1999). However, overall survival rates for this paediatric population have continued to improve over the years (Herrera et al. 2000), and more and more clinicians are facing the challenge to implant ECMO in these patients. According to a survey of 118 paediatric ECMO centres, 78% stated that malignancy was not a contraindication for ECMO, with only 17% and 5%, respectively considering it a relative contraindication or who would not offer ECMO to such patients. From 1997 to 2004 ECMO use in 107 children (73 HMs and 34 with solid tumours) was reported in the Extracorporeal Lung Support Organization (ELSO) registry (Gow et al. 2009); it was primarily required for respiratory support in 86 patients (80%) and lasted a median of 6.1 days. Overall survival to hospital discharge was 35% for those with HMs or solid tumours. Although this relatively low survival rate could be considered acceptable in light of these patients' notable disease severity, children with malignancies represent a wide spectrum of disease states and outcomes. Indeed, for a subpopulation of children undergoing haematopoietic stem-cell transplantation (HSCT), the prognosis seemed worse. Over a 22-year period, 29 HSCT patients were entered in the ELSO Registry: 21 (72%) required ECMO respiratory support and 8 (21%) needed ECMO cardiac support. Twenty-three (79%) patients died on ECMO and only 3 (10%) were discharged from the hospital (Di Nardo et al. 2014). These contrasting results, obtained for a mixed-case population of immunocompromised children, suggest offering ECMO on a case-by-case basis, with malignancy prognosis being an important factor.

> "ECMO in immunocompromised patients remains controversial"

Data on Adult Patients

The frequency of ECMO use for immunocompromised adults is unknown. For example, in the cohort of 2009 A(H_1N_1)-influenza–associated ARDS patients treated with ECMO, 19% were immunocompromised (Pham et al. 2013), representing 31% of the 140 cohort patients with ARDS of multiple aetiologies reported by Schmidt et al. (2013). In that cohort, the "immunocompromised" group comprised patients with HMs (30%), solid tumours (23%), solid-organ transplant (19%), high-dose or long-term corticosteroid and/or immunosuppressant use (19%), and HIV infection (9%). Only 32% were alive 6 months post-ICU admission. In addition, immunocompromised status was independently associated with death at 6 months post-ICU discharge (odds ratio 4.33 [95% confidence interval 1.55–12.12], p = 0.005) (Schmidt et al. 2013). Recently, Wohlfarth et al. reported the outcomes of 14 patients with HMs who received ECMO support for severe ARF in their centre (Wohlfarth et al. 2014). HMs were diagnosed in 4 patients during ECMO support. Five patients received their first chemotherapy dose on ECMO and 4 had undergone HSCT within the previous year. At ICU admission, their median (IQR) sepsis-related organ failure assessment (SOFA) score was 12 (11–13) and all patients received vasopressors; 11/14 were thrombocytopenic, with a median platelet count of 35 (26–51) G/L, and 5 were leukocytopenic, with a median leukocyte count of 2.1 (1.8–2.5) G/L. All HSCT recipients died, although 50% survived their ICU and hospital median (IQR) stays of 22 (21–77) days and 63 (49–110) days, respectively. Severe bleeding events were common (5/14, 36%). Thus, clinicians must strive to avoid any increment of risk factors for bleeding in this specific population. To achieve this goal, no or very low anticoagulation is strongly encouraged, especially when massive platelet transfusions are unable to restore safe platelet levels (Wohlfarth et al. 2014).

Because haemorrhage and nosocomial infections are the two main risks for immunocompromised patients treated with ECMO, developing new strategies to limit these risks is definitely the next stage to improve outcomes. To reach this objective, Hoeper et al. conducted a single-centre, uncontrolled pilot trial designed to assess the feasibility of venovenous ECMO in awake, non-intubated, spontaneously breathing ARDS patients, thereby avoiding invasive mechanical ventilation (Hoeper et al. 2013). Six patients with severe ARDS (maximum PaO_2/FiO_2 ratios of 100 mm Hg on noninvasive ventilation), 4 of whom were immunocompromised, were enrolled. After a mean of 7.5 days on ECMO, 4 patients were discharged from hospital; 3 of them had received ECMO alone without invasive ventilation.

Conclusion

Using ECMO in immunocompromised patients remains controversial due to the lack of strong scientific evidence for the benefit that this technique might afford these patients, as they, especially adults, develop more frequent and more severe ECMO-related complications. Pending results of large observational or randomised trials on immunocompromised patients, ECMO should be restricted to selected patients with at least a curative prospect of their immunodeficiency, except those with recent (< 3 months) cardiac transplantation, for whom it is essential. However, the markedly improved ICU survival

observed over 2 decades suggests extending ECMO use to this population. Results of the ongoing retrospective international Immuno-Deficiency and ECMO for Acute respiratory failure, the IDEA study (International ECMO Network 2016), should 1) provide a first detailed description of ECMO use in immunocompromised adults with acute respiratory failure; 2) identify the major complications arising in this specific population; and 3) describe the related ICU, hospital and 90-day outcomes for the whole population and specific immunodeficiency subgroups. ■

Abbreviations

ARF acute respiratory failure
ECMO extracorporeal membrane oxygenation
HIV human immunodeficiency virus
HM haematological malignancies
HSCT haematopoietic stem-cell transplantation
SOFA sequential organ failure assessment

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EXTRACORPOREAL LUNG SUPPORT IN TRAUMA PATIENTS

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The rationale, indications and challenges of extracorporeal lung assist in trauma patients with severe acute respiratory distress syndrome is given on the basis of clinical and scientific experience.

Traumatic lung injury is often present in multiple trauma with a wide spectrum of severity. In a large cohort study, patients with multiple trauma were reported to suffer from acute hypoxaemia in 64% of cases (Howard et al. 2015), 46% of whom developed the acute respiratory distress syndrome (ARDS) (Ferguson et al. 2012). ARDS is characterised by a life-threatening impairment of the pulmonary gas exchange, resulting in hypoxaemia, hypercapnia and respiratory acidosis and requiring acute rescue measures (intubation and lung protective mechanical ventilation, adequate positive end-expiratory pressure (PEEP), positioning manoeuvres). Therapeutic advantages in the critical management of severe trauma or thoracic injuries have been made, but these diagnoses present a challenge and are still associated with increased mortality and morbidity (Shah et al. 2008). Mechanical ventilation can damage the lungs and initiate an inflammatory response contributing to extrapulmonary organ dysfunction or triggering multiple organ failure. In trauma patients with critical respiratory insufficiency a benefit from rescue extracorporeal lung support (ELS) is discussed.

Technique and Rationale for Extracorporeal Lung Support

Venovenous extracorporeal membrane oxygenation (vvECMO) is used with an increasing tendency to avoid critical oxygenation impairment, and to reduce harm from ventilation in patients with severe ARDS (Del Sorbo et al. 2014). In principle, during ECMO a pump is integrated in an extracorporeal circuit after cannulation of two central veins. In this circuit an artificial membrane enables an extracorporeal gas exchange across the hollow fibres. vvECMO is indicated in patients with severe ARDS within 7 days after onset and with persistent life-threatening hypoxaemia despite optimised supportive therapy. Venovenous extracorporeal CO_2 removal (ECCO2R) is an ECMO technique that works at lower extracorporeal blood and sweep gas flows than vv– and avECMO, which is mainly used to avoid unacceptable hypercapnia or acidosis, as such preventing the need for injurious ventilator settings (Morimont et al. 2014). All ECMO techniques implicate certain haemodynamic effects and risks and their use requires expertise, experience, routine and an interdisciplinary approach (Combes et al. 2014). Possible complications include technical problems (clotting, air leakage, haemolysis) as well as bleeding due to cannula insertion or systemic anticoagulation. Despite the fact that technical advances have promoted safety and simplicity of extracorporeal lung support systems during the past few years, rigorous evidence of optimal indication, timing and management is still lacking. Nevertheless ECMO is increasingly being used as a rescue therapy in ARDS patients, and it might show a survival benefit in future randomised studies.

> “a promising and life-saving treatment option in severe post-traumatic ARDS”

Extracorporeal Lung Support in Trauma Patients – Scientific and Clinical Experience

Trauma patients with critical hypoxaemia and/or hypercapnic acidosis are at risk for pulmonary and cardiocirculatory failure, especially with concomitant haemorrhagic complications or anaemia. Furthermore, invasive mechanical ventilation in ARDS may induce harmful effects of high inspiratory pressure and lung overinflation to the right ventricle (Repesse et al 2015). Although there is a rationale for the use of ECMO in these clinical situations, ECMO is seen as an invasive measure with potentially severe complications, and in the early posttraumatic period patients are in a fragile balance at risk of haemodynamic instability or shock. In recent years, the feasibility and efficacy of ECMO in severe posttraumatic ARDS was described by a few observational studies (a synopsis is presented in **Table 1**). Cordell-Smith et al. published a retrospective analysis of a cohort of 28 trauma patients with long bone fractures, blunt chest trauma or combined injuries referred to a single tertiary centre for ECMO support (Cordell-Smith et al. 2006). The survival rate in this group was 71.4%. The experiences of the Regensburg ECMO group were reported in 2013 (Ried et al. 2013). 52 trauma patients with a mean age of 32 ± 14 years suffering from severe thoracic trauma and ARDS were provided with pumpless arteriovenous extracorporeal lung support (PECLA n=26) or with vvECMO (n=26). After applying ELS critical hypoxaemia and hypercapnia were resolved immediately and the parameters of mechanical ventilation were reduced in order to perform lung protective

ventilation. The mean duration of ELS support was 6.9 ± 3.6 days. During ECMO treatment numerous thoracic and non-thoracic surgical procedures were necessary, but in this series no relevant life-threatening bleeding complications were observed. Similarly Guirand et al. reported data from two American College of Surgeons-verified level 1 trauma centres (Guirand et al. 2014). Trauma patients were divided retrospectively into a cohort of hypoxaemic patients, who received vvECMO after failure of 'conventional' rescue (n=26), and into a patient group managed with mechanical ventilation (n=76). In a matched-pair analysis the adjusted survival rate was greater in the ECMO group (adjusted OR 0.193, p=0.034), but ECMO patients received more transfusions and had more bleeding complications. Finally the recent analysis of the Extracorporeal Life Support Organization (ELSO) database on ECMO in 85 trauma patients (Jacobs et al. 2015) demonstrated a survival to discharge of 74.1%. The general conclusion was that the use of ELS might be advantageous in patients with post-traumatic ARDS. An algorithm for the use of ECMO in trauma patients is given in **Figure 1**.

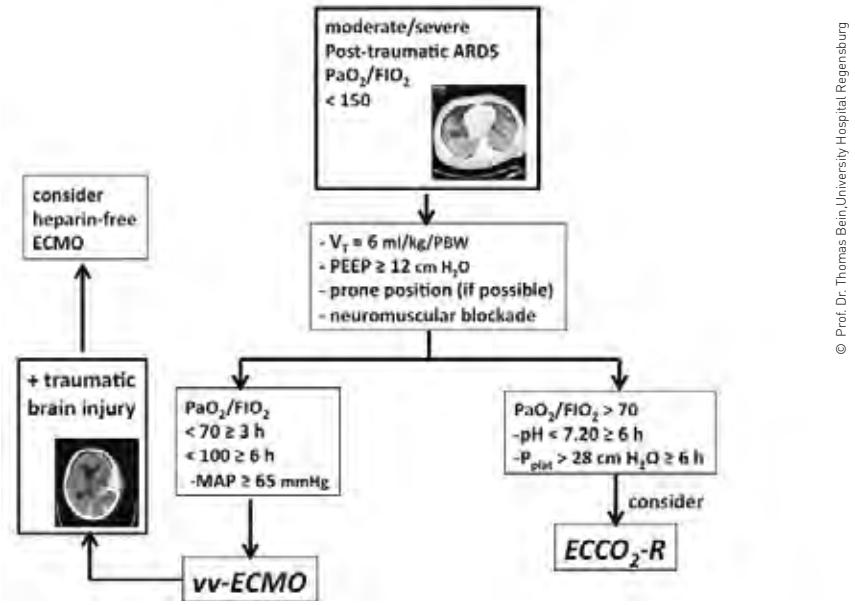

Figure 1. Algorithm for indications to ECMO/ECCO2-R in patients with severe posttraumatic ARDS. (conformed to Richard et al. 2014)
VT = tidal volume, TBI = traumatic brain injury.

Practical Aspects and Clinical Challenges

The use of ECMO in trauma patients is associated with specific requirements and possible problems. It is a challenge for a high-level trauma centre. Some practical aspects and specific clinical strategies must be considered and should be reflected in an algorithm for the ICU team (**Table 2**).

Haemodynamic Monitoring and Therapy

Haemodynamic monitoring includes continuous monitoring of arterial blood pressure, repeated echocardiography and continuous recording of extracorporeal blood flow. Of note, pulse contour analysis-based or continuous thermodilution-based cardiac output monitoring are not recommended in patients under ECMO, since the first may underestimate cardiac output (Haller et al. 1995), and the second may lead to erroneous results caused by indicator loss into the extracorporeal circuit (Rauch et al. 2002). Accurate record of the cumulative fluid seems important, since a positive cumulative fluid balance has been identified as one independent predictor of worsened outcome of ECMO patients (Schmidt et al. 2014).

Haemodynamic therapy requires a special and careful approach regarding volume replacement and vasopressor use. Volume overload could worsen lung oedema, which in turn worsens outcome. On the other hand hypovolaemia may induce vein collapse with extracorporeal blood flow, causing so-called cannula 'suctioning' and 'chatter' that may result in haemolysis (Choi and Nam 2008). Therefore haemodynamic support is optimised by a balanced strategy of fluid infusions (small boluses, e.g. 250 ml) and vasopressors (continuously titrated norepinephrine) under repeated monitoring (mean arterial pressure, echocardiography, central venous oxygen saturation [$ScvO_2$], lactate).

Table 1. Important Observational Studies on the Use of Extracorporeal Lung Support in Trauma Patients

Author/Year	Methods/Patients	Intervention	Complications	Survival rate
Cordell-Smith 2006	retrospective: 28 ISS = 46 PaO_2/FIO_2 = 62	vvECMO	not reported	71.4%
Ried 2013	retrospective:52 ISS = 59±10 PaO_2/FIO_2 = 63 (49-101)	PECLA: 26 vvECMO: 26	cannula-related 15 %	79 %
Guirand 2014	retrospective, matched-pair:102 ISS = 29±12 PaO_2/FIO_2 = 50±10	vvECMO: 26 conv: 76	haemorrhagic: -vvECMO: 15 % -conv: 1 % (p=0.014)	vvECMO: 58% conv: 55 % (p=0.034)
Jacobs 2015	retrospective ELSO-database: 85 PaO_2/FIO_2 59±3	vvECMO	haemorrhagic: 29.4 %: - surgical site 14.1 % - cannula-related 18.8 %	74.1%

ELSO Extracorporeal Life Support Organization FIO_2 fraction of inspired oxygen ISS Injury Severity Score PaO_2 partial pressure of oxygen PECLA pumpless extracorporeal lung assist vvECMO venovenous extracorporeal membrane oxygenation

Systemic Anticoagulation

The demand for systemic anticoagulation to prevent circuit clotting might favour bleeding complications. On the other hand continuous technical advances (heparin-coated circuits, centrifugal pump) have reduced the required doses for anticoagulation and allowed use even in severe trauma patients with bleeding shock (Arlt et al. 2010). In the Regensburg ECMO Centre experience (Ried et al. 2013) the continuous anticoagulation with heparin was balanced, aimed at a target partial thromboplastin time (aPTT) ≈ 50 sec, and no severe bleeding complications — even under thoracic

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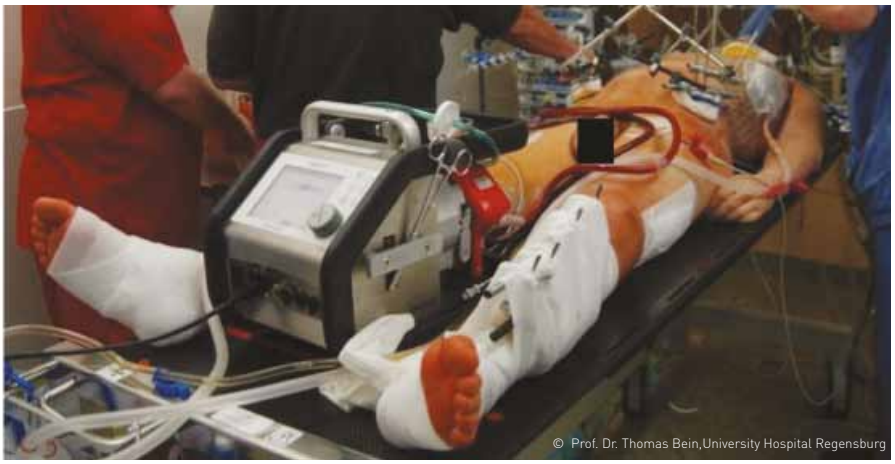

Figure 2. Multitraumatised patient with a compact ECMO device in preparation for a CT scan. Note the two ECMO tubes with venous and oxygenated blood

Table 2. ECMO in Trauma Patients: Practical Aspects and Specific Problems

Measure	Practical aspect	Problem/comment
Haemodynamic monitoring	Mean arterial pressure, extracorporeal blood flow, echocardiography	Thermodilution-based or pulse contour analysis-based cardiac output monitoring not recommended (indicator loss into circuit)
Anticoagulation	Low-dose-heparin: ≈ 8 IU/kg/h, aPTT ≈ 50 sec	Small balance between prevention of clotting and avoidance of bleeding complications
Intra-hospital transportation	Support by experienced staff, enough battery packs	Safety aspects, longer periods without current
Damage-control surgery	ECMO-handling in the operating theatre, volume balancing	Haemodynamic stability, volume replacement

aPTT activated partial thromboplastin time

and non-thoracic surgeries — were observed. The median demand of packed red blood cells was 3 (range 0-54) during the ECMO period. In patients with severe ARDS, who are suffering from traumatic brain injury and intracranial bleeding, ECMO therapy is considered to be contraindicated due to limited systemic heparinisation. On the other hand these patients might benefit from ELS to avoid hypercapnia (increase of intracranial pressure) and deleterious ventilation. The use of prolonged heparin-free ECMO was reported in three multiple-injured ARDS patients with traumatic brain injury (Muellenbach et al. 2012), and neither ECMO-associated bleeding nor clotting of the extracorporeal circuit occurred. Such a heparin-free ECMO strategy might be considered individually under specific rescue conditions in an interdisciplinary round.

Intrahospital Transportation and Damage Control Surgery

In the early post-traumatic period patients frequently need transportation from the intensive care unit to diagnostic (e.g., CT scan, interventional radiology, **Figure 2**) or therapeutic procedures (damage control surgery, neurosurgery, laparotomy). In ECMO patients these transportations and procedures are at special risk of ECMO-related or general complications and they require special preparation and realisation. The following safety aspects and recommendations are given (Day 2010):

- trained accompanying staff (1 physician, 2 nurses), possibly perfusionist;
- power of battery packs ≥ 2 hrs;
- oxygen supply reserve;
- safe mode of controlled mechanical ventilation;
- a hand crank for the case of power problems;
- vasopressors, rescue drugs;
- safe chest tube management;
- rescue devices (unintended extubation).

For surgery procedures a careful balance between volume replacement and avoidance of fluid overload must be ensured by experienced anaesthetists. Systemic anticoagulation should be stopped for surgery. In the scenario of the operating theatre, the ECMO cannulae are included in a sterile covering and special attention is required to avoid accidental removal. The results from recent observational studies (Cordell-Smith et al. 2006; Ried et al. 2013; Guirand et al. 2014; Jacobs et al. 2015) show that diagnostic and therapeutic procedures are associated with a low complication rate.

Conclusion

The technique of extracorporeal lung support is a promising and life-saving treatment option in severe post-traumatic ARDS. ELS enables a rapid and sustained improvement of critically impaired gas exchange and the correction of severe acidosis, and additionally can provide lung protective ventilation. Utilisation of ELS in multiple trauma patients is associated with an acceptable complication profile, but a specific expertise, routine, and an interdisciplinary approach are needed.

Conflict of Interest

Thomas Bein received honoraria for lectures and for the membership of the Medical Advisory Board of Novalung Company, Heilbronn, Germany. ■

Abbreviations

ARDS Acute respiratory distress syndrome
ECMO Extracorporeal membrane oxygenation
ELS Extracorporeal lung support
PECLA Pumpless extracorporeal lung assist
PEEP Positive end-expiratory pressure
$ScvO_2$ Central venous oxygen saturation

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ADVERTORIAL

CLOSE MONITORING OF ECMO PATIENTS WITH A PATIENT DEDICATED BLOOD GAS ANALYSER

IN-LINE BEDSIDE BLOOD GAS ANALYSIS ENABLES RAPID RESULTS FOR RESPIRATORY SUPPORT MANAGEMENT

Extracorporeal membrane oxygenation (ECMO) is an acute support system used to aid heart and lung function in patients with severe respiratory or cardiac failure. Having its origins in the operating theatre, the use of ECMO has now migrated into the ICU. Since the mortality risk of ICU patients with ECMO, such as those with acute respiratory distress syndrome (ARDS) is extremely high, close monitoring of these patients is essential to assess the state of their lungs and to prevent further damage.

Various devices are available to monitor pressures, flow, and temperature of the ECMO blood and gas circuits, as well as physiological variables in the patient. However, there are current limitations in measuring blood gases, which are required frequently in order to effectively monitor the adequacy of gas exchange support.

The need for results immediacy

The primary purpose of measuring blood gases (as opposed to online saturation) is to determine both inlet and outlet pCO_2 to evaluate membrane lung function, as well as blood pH for metabolic status determination. Should CO_2 elimination remain inadequate, this can result in severe respiratory acidosis [1]. Consequently, immediate return of blood gas results and frequent measurements are essential in the management of patients with ECMO. Such results are also just as essential when weaning patients from ECMO.

Current methods of blood gas analysis require arterial blood sampling from an appropriately located catheter or the circuit, which can: only be undertaken intermittently, meaning that there may be delay in response to changes in the patient's physiological status; have a significant turnaround time, as blood samples are transferred to a central analyser; expose the health-care professionals to the patient's blood; and result in iatrogenic blood loss [2].

A monitoring system that addresses all of the aforementioned limitations has recently been developed by Sphere Medical (Cambridge UK). Uniquely, the Proxima miniaturised in-line analyser enables the rapid and frequent delivery of blood gas results directly at a patient's bedside. This then aids early decision-making and ensures closer control of therapy, including ECMO. When a blood gas measurement is required, blood is withdrawn from the patient directly into the Proxima Sensor without the need to take a sample and walk away for analysis. Results are then displayed at the patient's bedside monitor within three minutes.

Conserving blood

Bleeding is the most common complication during ECMO due to systemic anticoagulation, thrombocytopenia, and thrombocytopathia [1]. Patients on ECMO require frequent transfusions, which can in turn modify coagulation status and require further titration for coagulation management. The use of greater amounts of RBC among patients supported with ECMO for non-cardiac indications are independently associated with significant morbidity [3].

Therefore, minimisation of blood loss and avoidance of subsequent red blood cell transfusions is important in these patients. With diagnostic testing being a significant factor in cumulative blood loss, the use of a patient dedicated arterial blood gas analyser would ensure blood conservation [4].

Proxima uses a closed sampler device which allows return of the discard volume to the circulation whilst maintaining a closed system. Once the sample has been analysed directly by the in-line Proxima Sensor, all blood is returned to the patient resulting in zero blood loss. This is not only key to avoidance of iatrogenic blood loss, but also to enabling unlimited blood gas sampling.

Minimising infection risk

ECMO is an intervention that may carry the risk of infection, particularly if ECMO is used in immunocompromised patients. Since frequent arterial blood sampling is necessary, a key aspect of infection prevention and control with such patients is the stringent management of their blood samples, particularly during collection and transportation for analysis.

As a patient-dedicated, closed system, Proxima keeps infection control simple and effective, whilst also minimising the number of openings of the arterial line for sampling. This protects both the patient's blood from exposure to blood stream infections, as well as the caregiver by limiting exposure to blood borne pathogens during the course of routine patient care. Furthermore, by avoiding transfer of blood to a central blood gas analyser, Proxima also reduces blood handling and therefore cuts risk of infection transmission. Additionally, as all blood is returned safely to the patient, this avoids the need for waste management of potentially infected blood specimens and syringes.

For more information on how Proxima enables fast response, proactive critical care, such as for patients on ECMO, by delivering rapid results for blood gas exchange, please visit www.spheremedical.com.

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SPHERE
RAISING THE STANDARD OF CRITICAL CARE

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LUNG PROTECTIVE VENTILATION

TWINSTREAM® PULSATILE BI-LEVEL VENTILATION (P-BLV)

The Twinstream® ventilator (Carl Reiner GMBH, Vienna, Austria) is an electric-driven microprocessor-controlled jet ventilator, which allows simultaneous application of two different jet streams (low frequency and high frequency), resulting in a pulsatile Bi-Level Ventilation (p-BLV) mode. *ICU Management & Practice* spoke to Prof. Dr. Gerfried Zobel about his experiences with the system in the Paediatric ICU at the Children's Hospital in Graz, Austria.

Which patient groups could potentially benefit from pulsatile Bi-Level Ventilation (p-BLV)?

In the Paediatric ICU infants and children with ARDS, SARS, SARS-like disease with occluded airways, plastic bronchitis, pulmonary barovolutrauma, thoracic trauma, and burn inhalation injury.

How would you summarise your experience with this technology?

Pulsatile-BLV using the Twinstream ventilator significantly increased the clearance of airway debris and secretions associated with improved gas exchange in infants and children with different forms of acute hypoxic acute respiratory insufficiency.

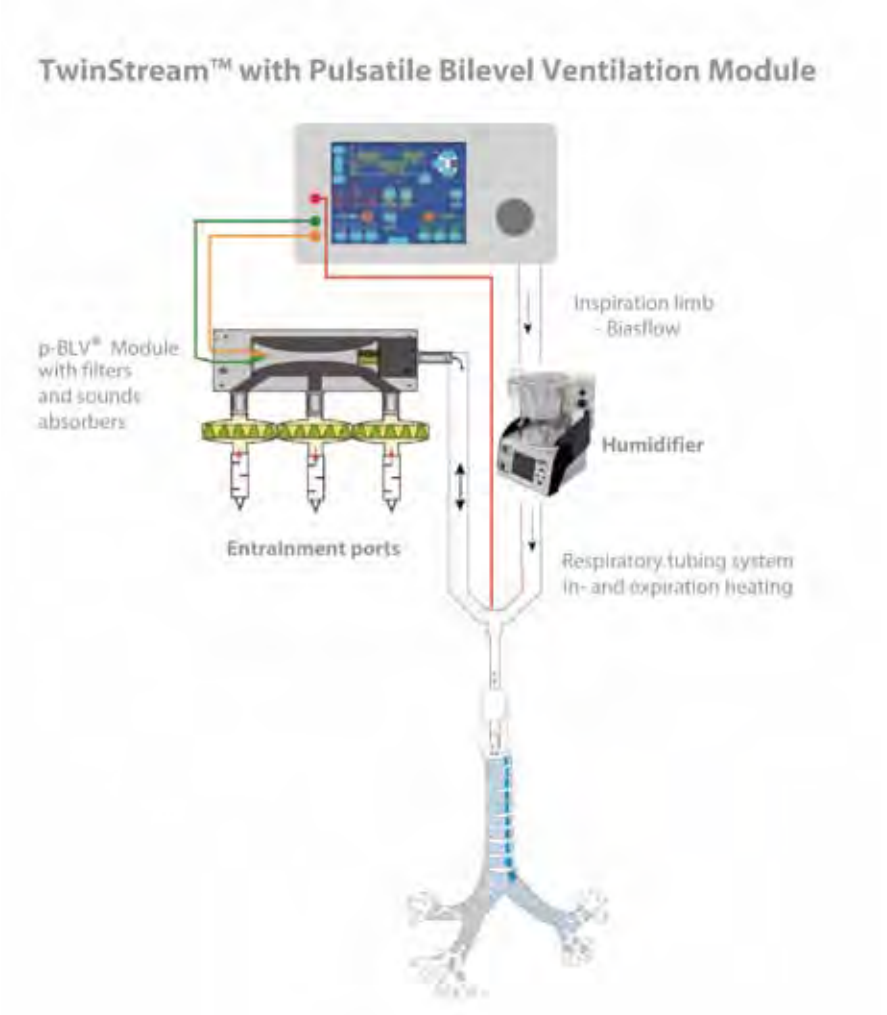
Hypoxaemia is a common finding in the paediatric intensive care unit and may result from paediatric acute lung injury/paediatric acute respiratory distress syndrome (P-ALI, P-ARDS), infection, sepsis and postoperative complications. In addition, these infants and children may have problems with airway secretions. These patients frequently do not respond to standard ventilatory techniques and additional therapies such as inhaled nitric oxide, inhalation, prone positioning and recruitment manoeuvres. Hence our decision to use a jet ventilation system.

How does this technology differ from conventional mechanical ventilation approaches and what are its advantages?

A variable bias flow warmed and humidified in the inspiratory limb of the breathing circuit reaches the y-piece connected to the endotracheal tube. The expiratory limb of the breathing circuit is connected with the p-BLV module® and the inspiratory bias flow is modified by two jet streams, resulting in an oscillating gas column to the patients' airways. In addition the p-BLV module® acts as a pneumatic-driven PEEP generator (See image).

Would you recommend using this technology as an alternative / supportive therapy to ECMO?

Use of Pulsatile BLV might avoid the need for ECMO support and it might improve mobilisation of airway secretions on ECMO, eventually resulting in shorter periods on ECMO.



Would you share with us a patient case where pulsatile Bi-Level Ventilation (p-BLV) has made a difference?

Case Report

Down syndrome with congenital heart defect
Ventricular Septal Defect closure 2002

Actual history

13-year old girl, fever, coughing, wheezing, increasing fatigue, tachy-dyspnea
Chest x-ray:
overinflation, signs of bronchitis and peribronchitis
Inflammatory parameters: Leukocytes: 35.87 G/L, CRP: 113 mg/L

Therapy

Bronchodilators
Intravenous steroid application
Oxygen application

Transfer to PICU

Silent lung in flat position
Massive wheezing in sitting position
Oxygen therapy 8L/min → SpO_2: 85-90%
Agitation
Exhaustion despite noninvasive ventilation (NIV) support
Sedation-Analgesia → Endoscopic intubation (6.5 mm+cuff) and invasive mechanical ventilation
Antibiotic strategy: Cefuroxime, clarithromyxin

Mechanical ventilation

Noninvasive mechanical ventilation (NIV)
NIV 6 hours
Invasive mechanical ventilation 14 days
Conventional mechanical ventilation - 281 hours
Pulsatile bilevel lung ventilation - 37 hours
Weaning - 25 hours
Extubation
Postextubation period
NIV - 4 hours
High flow nasal cannula (HFNC) - 12 hours
Adjuvant therapy-Inhalation
Initially salbutamol inhalation – side effects: tachycardia, hypotension
Mucoclear 3 and 6% inhalation: every 3 to 4 hours
Deoxyribonuclease (Dnase) nebulisation every 12 hours
Inhaled r-tPA every 6 hours
Endoscopic lavage 3x
Systemic steroid medication

Diagnosis

Mycoplasma pneumonia with acute hypoxic respiratory failure
Tenacious secretions
Inflammatory bronchial casts
Multiple atelectasis and regional overinflation
Ventilation/perfusion imbalance
Intrapulmonary right to left shunts
Diffusion limitation

Pulsatile BiLevel Ventilation-pBLV

Improved mobilisation of tracheo-bronchial mucous casts
Reopening of atelectasis
Improvement of V/Q mismatch
Improved oxygenation
Adequate CO_2-elimination

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EUROPEAN PERFUSIONISTS IN ECLS/ECMO

ROLES & RESPONSIBILITIES

Since its first clinical use in the 1950s, the set-up and management of the heart-lung machine (HLM) has been the responsibility of the perfusionist, who has a documented competency in every facet of extracorporeal technology because of their theoretical and practical training. In contrast, when this technology leaves the operating room to provide longer-term support in terms of ECLS (extracorporeal life support) or ECMO (extracorporeal membrane oxygenation), there is no longer worldwide uniformity nor consensus concerning clinical roles or responsibilities. It is clear that certain involvement from the extracorporeal technology specialists is required to provide quality ECMO care, but the extent of their involvement has been undefined within Europe. As it was unclear how intensely perfusionists around Europe are involved in ECLS, a survey was created inquiring about their roles and responsibilities in local ECMO programmes.

Staffing Roles in ECMO Programmes – Historical Growth

ECLS systems are composed of mechanical devices designed to temporarily take over the pump function of the heart and gas exchange function of the lungs. Although based on the same technology as the HLM, which is used during open heart surgery, these ECLS devices have different features to enable more long-term support and to allow more distant supervision. Many ICUs have started an ECMO programme with various success, depending on the indications but also on their training, expertise and type of multidisciplinary collaboration (Paden et al. 2014).

The term "ECMO specialist" was introduced in the U.S., referring to the person specialised in taking care of the patient on ECMO, and each institution had its own unique training for these individuals. In a 2008 survey of North American ELSO centres' team roles, it was identified that these ECMO specialists came from a variety of departments; they were nurses, respiratory therapists, perfusionists or physicians. The degrees of involvement of perfusionists varied depending on their ability to handle both cardiac surgical cases and ECMO cases outside the operating room, and therefore other disciplines were forced to take over some of the roles perfusionists were trained for so intensely. It was not uncommon that in respiratory ECMO centres nurses were trained to become ECMO specialists, while cardiac ECMO remained mostly under the supervision of the perfusionist (Lawson et al. 2008).

To provide support to institutions delivering ECLS, the Extracorporeal Life Support Organization (ELSO) was founded in the USA in 1989. ELSO has established an observational data registry, offers a platform supporting education, training and research, provides practice guidelines and organises international ECMO meetings. Broad multidisciplinary participation is strongly encouraged by ELSO without identifying or defining responsibilities (elso.org).

Within Europe, ECMO as an adjuvant therapy in both respiratory and cardiac support remained controversial for many years, especially as no evidence of superiority above conventional treatment was found in the few randomised trials, except in neonatal respiratory ECMO. Only due to the isolated successes reported in case series were there ongoing but variable efforts to place patients on ECMO, mostly when the entire treatment arsenal was exhausted. Thanks to the reappraisal of ECMO as a temporary solution in patients in cardiac failure, and with the positive outcome of the Cesar trial in adult respiratory failure (Peek et al. 2009), centres started to reconsider putting patients on ECMO. The Influenza A (H1N1) pandemic pushed many who were still considering over the edge and since 2009 we have experienced a boom in ECMO in ICUs all over Europe (Paden et al. 2014).

> "Isolated respiratory units experience more difficulties setting up a quality ECLS programme"

Because of the struggling growth and also because of the regulatory and historical differences with the U.S., not many centres within Europe were initially interested in joining ELSO. With the rapidly growing interest in ECMO in the last few years, a European chapter of ELSO (EuroELSO) was founded in 2011 to offer more relevant support and a platform for European ECMO centres. Since the establishment of EuroELSO, the registration of European centres has rapidly grown (**Fig. 1**). 78 European ECLS centres from all over Europe are registered and can seek ELSO support (2015 figure).

Perfusionists' Role in ECLS Centres – Results of a European Survey

To identify how intensely perfusionists around Europe are involved in ECLS programmes,

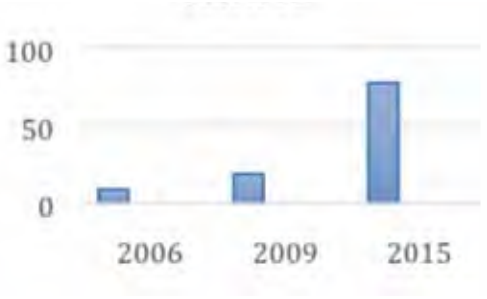


Figure 1. No. of European ELSO Registered Centres

a survey was created with SurveyMonkey (Vercaemst 2015). The survey was sent, starting in May 2014, to the delegates of all European countries that are members of the European Board of Cardiovascular Perfusionists (EBCP) with the request to forward it to the Perfusion Department of each cardiac surgery centre within their country. There was a good response overall from all over Europe; apart from Greece and Spain, who had some problems forwarding the survey towards their ECLS units, all EBCP countries responded (**Fig. 2**).

A total of 199 centres from 20 countries responded to the survey; of the responding centres 70% had an active ECLS programme; nearly 20% intend to start in the near future.

Only the current 135 and 34 ECLS centres starting in the near future were asked to complete the entire survey.

Asked if their centres are ELSO-registered, only 23% could confirm and only 14% were aware of their data being sent to the ELSO Registry (**Fig. 3**).

The main reason for this limited involvement seems to be lack of information about EuroELSO and its Data Registry and lack of awareness concerning its value in daily practice. Some respondents also expressed the concern for needing patient consent to be legally allowed to submit data.

All active and future centres were first asked a few questions concerning size and type of their centre (**Fig. 4 & 5**), and the answers indicated that ECMO remains an infrequently instituted therapy thus making it hard to gain routine experience and expertise.

The answers to the survey questions concerning clinical roles (**Fig. 6 & 7**) revealed the important clinical involvement overall of perfusionists—from setting up and priming the circuit until weaning off the ECLS. In nearly 20% of centres, the perfusionist remained bedside 24/24hrs to monitor the circuit. Many centres started up an ECMO programme while experiencing a busy cardiac surgery programme, hence the restrictions some centres have in making perfusionists available outside the operating room.

If not present at the bedside 24/24hrs, the perfusionist visits the ECMO patient on a regular basis to check the circuit and optimise circuit settings. Also for technical troubleshooting a perfusionist is available 24/24.

In most European ECLS centres, physicians are clearly participating in some tasks, while nurses' roles remain limited to patient rounds and data entry. In contrast to the U.S., there seems to be little involvement of the so-called

Figure 2. Responding European Countries

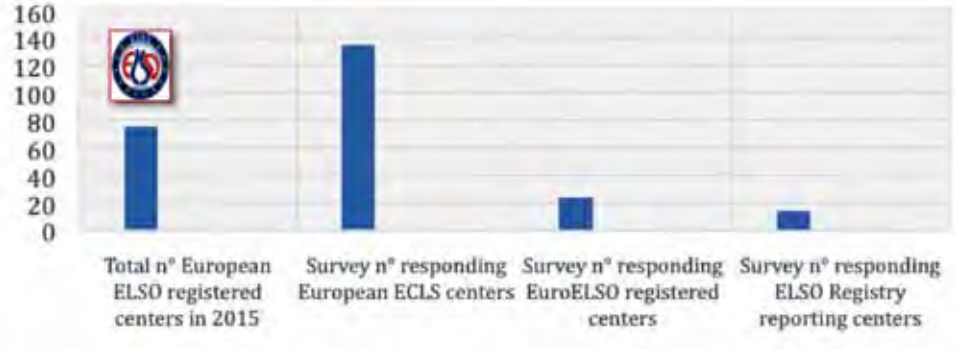


Figure 3. EuroELSO Registered vs European ECLS Centres

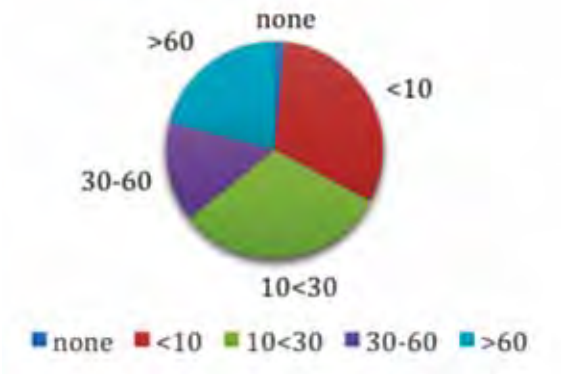


Figure 4. Annual ECMO Runs/centre

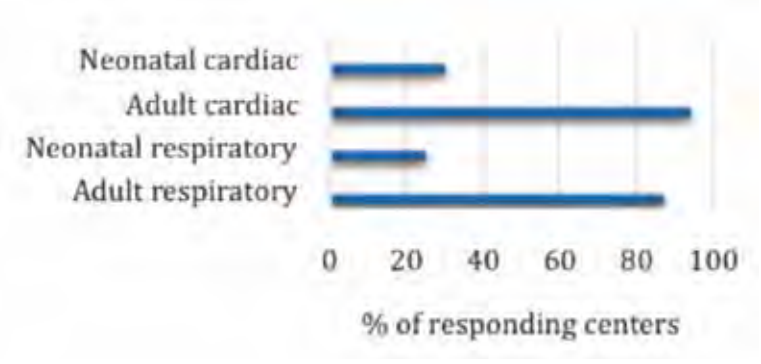


Figure 5. Which type of ECMO support is being offered in your centre?

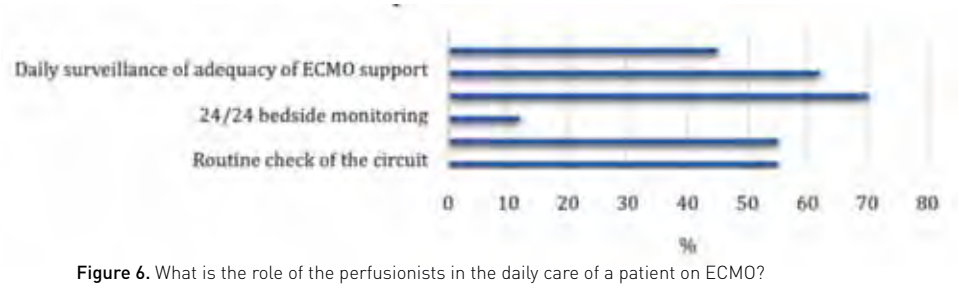


Figure 6. What is the role of the perfusionists in the daily care of a patient on ECMO?

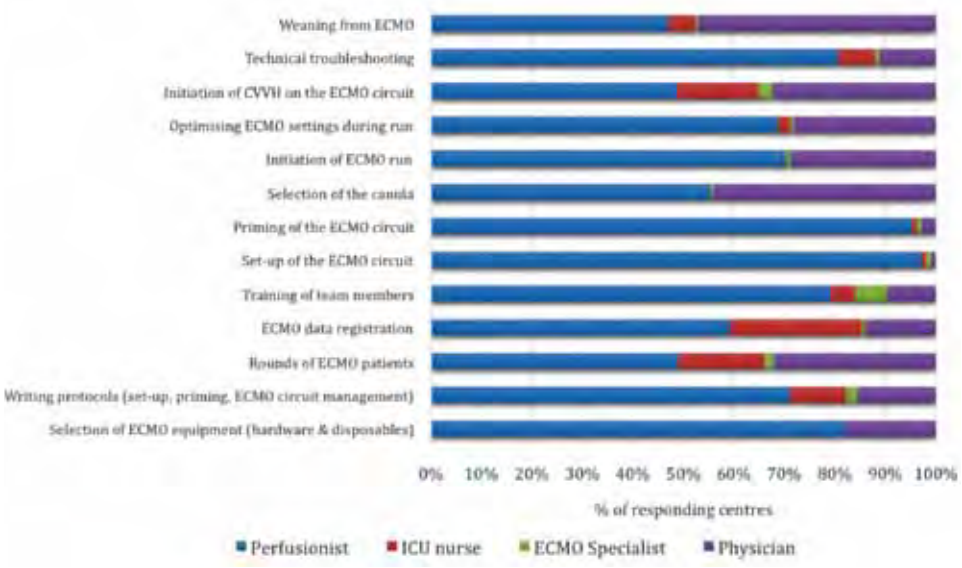


Figure 7. Who is responsible for the following ECMO related tasks in our centre?

'ECMO specialists' or at least this terminology is not adapted by many European centres. Only very few centres indicated the involvement of an ECMO specialist, and those who did were asked to define the background of this person. In half of these cases this referred to an "ICU nurse with a specialty ECMO training"; the other half referred to "Perfusionists with extensive experience in ECMO".

Most centres report the same involvement of perfusionists in cardiac as in respiratory ECMO, but it is unclear who takes this involvement in the non-cardiac surgery centres without perfusionists as these centres were not addressed for the survey (**Fig. 8**).

In many countries there seem to be no legal restrictions in setting up cardiac or respiratory ECMO programmes, hence the reason for the increased amount of small ECMO volume centres all over Europe (**Fig. 9**).

The majority of centres stated that additional training for perfusionists, physicians and nurses should be compulsory before starting up an ECMO programme and also that there should be support from an expert ECLS centre.

Most perfusionists agreed that there should be "Minimum Standards of Care'" established to which all ECLS centres should adhere. These Minimum Standards of Care would be written minimum requirements concerning staffing, training, experience, equipment, safety and so on, in order to optimise quality of ECLS programmes.

Discussion

From the results of the survey, it is clear that perfusionists within Europe have an important involvement in their in-house ECMO programme. There seems to be a variety of responsibilities once ECMO is initiated, but unlike in the U.S. there is little mention of nurses or ECMO specialists involved in the technical part of the ECMO programme.

The survey did not address the isolated respiratory ECMO programmes, which are set up in hospitals without a cardiac programme, so it is unclear who takes over the technical support in those centres. Isolated respiratory units experience more difficulties setting up a quality ECLS programme, as the absence of a cardiac surgery programme is a significant barrier to the development of an ECLS programme. There are such centres that have successfully initiated an ECMO programme with a smooth learning curve, but they need a well-organised, intensive and interdisciplinary training curriculum with well-defined roles and responsibilities (Sanchez-Glanville et al. 2015).

The survey also did not address non-specialised, peripheral centres putting their in-house patients on urgent ECLS with the help of a trained in-house or external team. It is not sufficient to have a trained physician to place the cannula and a specialist to prepare the circuit and initiate the ECMO therapy. The most challenging part is not to initiate, but to wean from ECMO, which can only be achieved if the failing organs are allowed to recover while providing efficient support. If physicians choose to start an ECMO treatment in a non-specialised centre, they owe it to the patient to transport him or her to an ECMO specialist centre for specialised supervision and optimal multidisciplinary care (Combes et al. 2014).

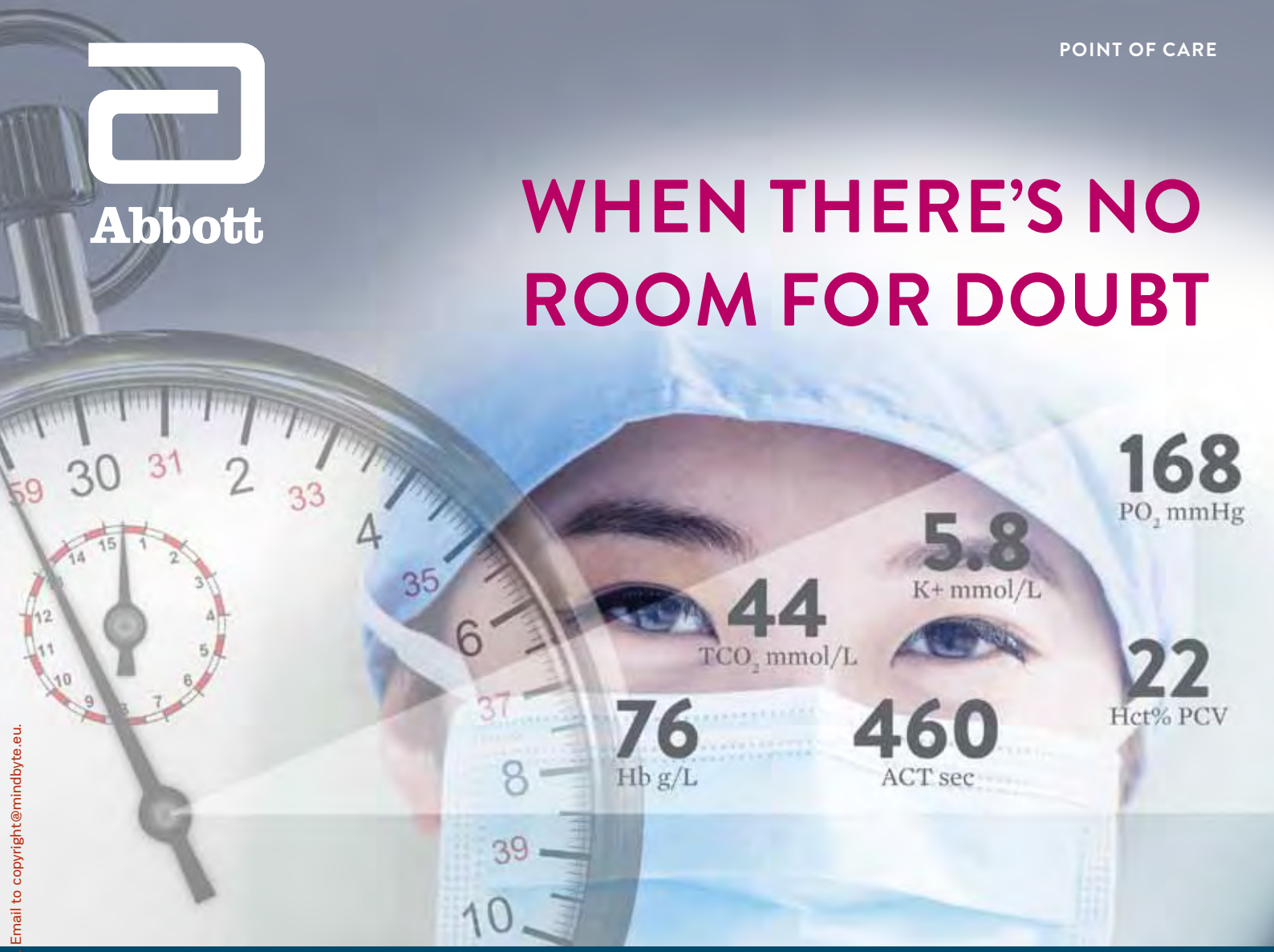
Whether 24/24hrs bedside technical support is needed depends upon the availability of a perfusionist, but also upon the experience and knowledge of the bedside caregiver. Staffing models in experienced centres with good outcomes prove that with the right training, it is possible to give safe and quality care to the patient on ECMO without a bedside perfusionist, on condition that there is a 24/24hrs on-call service for technical backup (Beckmann et al. 2011). Ideally, ongoing practical training with simulation training should be part of the training curriculum so that in the worst case scenario, telephone guidance should be sufficient to assist the bedside caregiver for urgent troubleshooting.

Staffing models might also differ depending on the volume of ECMOs performed. Recent data demonstrated significant better outcomes in centres which perform more than 20-25 cases a year as opposed to those with fewer than 20 ECMO cases a year (Combes et al. 2014). Maintenance of technical skills might be difficult in the low volume centres, and here a more close cooperation with the perfusionist is required to maintain a safe and quality ECMO programme (Mongero et al. 2013).

POINT OF CARE

Abbott

WHEN THERE'S NO ROOM FOR DOUBT



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- But an anaesthetic assistant can spend up to 20% of a procedure out of the room running gases*
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Reference:
1. Ojito JW et al. J Extra Corpor Technol 2012;44:15-20.

CVOR: cardiovascular operating room

* Assumes eight arterial blood gas (ABG) tests being run in a four-hour operation and travel time to and from the blood analyser outside of the CVOR. Excludes delays due to human factors, or any equipment delays

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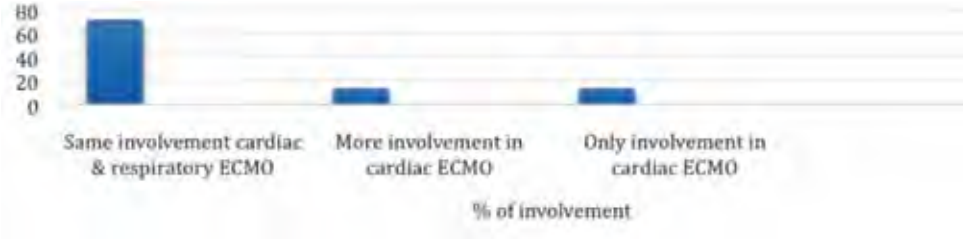

Figure 8. Is there a difference of involvement of the perfusionist in respiratory or cardiac ECMO? (in case your centre offers both types of ECMO support)

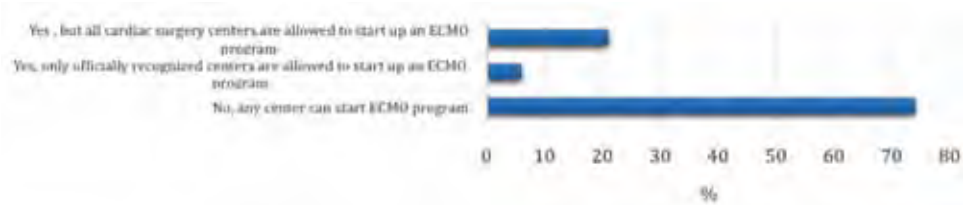

Figure 9. Are there any restrictions in your country in starting up any (respiratory or cardiac) ECMO programme?

Larger centres still report a significant number of ECLS-related complications, so there is still room for improvement (ELSO 2016). Not only survival but most importantly quality of life should be the focus. Support-related complications must be kept as low as possible. Late diagnostics of failing circuit parts often cause hazardous and complicated change-outs. Support needs to be evaluated on a continuous basis as inefficient support can be detrimental for the patients. Taking over too little ventricular function can result in multi-organ failure while seemingly sufficient support can destroy the patient's left ventricle permanently. Aggressive forces can lead to blood cell destruction with toxic end products, and anticoagulation disturbances can clot off the circuit or cause patient bleeding. These are only a few examples of complications, which can be minimised with trained bedside personnel supervising the patient.

ELSO recommends the assignment of an ECMO director to take medical responsibility for the programme and an ECMO coordinator to assist the ECMO director in safeguarding the quality of the programme. The role of ECMO coordinator is an important role requiring an intensive commitment, which might not be possible for all team members. In 2014, from the 81 European ELSO registered centres, 6 ECMO coordinators were certified perfusionists, 49 were medical doctors and most of the remaining 26 were registered nurses (Vercaemst 2015). Depending on the size of the ECMO programme, the job of the coordinator might require different investments, but there needs to be some official time allocation for whoever is assigned this job.

Conclusion

1. There is no standard of care that addresses ECLS personnel, training and programme structures, but it is clear that a successful ECLS programme needs multidisciplinary involvement, guidelines and defined roles.
2. ECLS circuitry is complex both in set-up and in major troubleshooting and therefore should remain the responsibility of the perfusionist. European perfusionists play an important, mainly technical supportive role in local ECLS programmes, but rarely offer a 24/24hrs bedside service, hence the importance of a well-trained bedside caregiver.
3. It is essential and beneficial for the patients' total approach that everyone on the team receives specialised training about all aspects of ECLS. As extracorporeal support technologies are the core business of perfusionists, technical training should ideally be provided by the perfusionist.
4. Each ECMO centre aiming at quality care should appoint an ECMO coordinator to assist the medical ECMO director with organising and implementing the training of the ECMO team, staffing, team meetings, quality improvement, protocol writing, maintaining equipment and supplies, and ensuring that data are entered into a database.
5. There are still many ECMO-related complications reported, so in-house data should be evaluated on a regular basis and preferably be benchmarked against the outcomes of experienced centres. Worrying results should be analysed and expert advice should be sought.
6. European ECLS programmes still lack involvement in ELSO, which offers important support to ECMO centres. ■

Abbreviations

EBCP European Board of Cardiovascular Perfusion
ECLS extracorporeal life support
ECMO extracorporeal membrane oxygenation
ELSO Extracorporeal Life Support Organization
HLM heart-lung machine

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BIOMARKER GUIDED ANTIBIOTIC THERAPY

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The aim of the present review is to summarise the current evidence for the use of biomarkers in facilitating therapeutic decision-making by guiding and tailoring the prescription and the duration of antibiotic therapy. The main benefits of this strategy are a potential reduction of antibiotics overuse in critically ill patients.

Overuse of antibiotics and its consequences represent a big challenge for healthcare services worldwide. One reason is the change in profile of inpatients observed during the last decades: they are increasingly older, have more comorbidities and are frequently immunosuppressed (Zuckerman et al. 2007). As a consequence, multidrug-resistant organisms are becoming very common as the aetiology of healthcare-associated infections (Martin-Loeches et al. 2014), and frequently these pathogens are isolated in patients with infection acquired in the outpatient setting. Therefore, we have in combination the difficulty of prescribing antibiotics to more vulnerable hosts with more difficult to treat infections. Clinical signs and symptoms are in general of limited value. As a result the prescription of antibiotics, often a combination of broad-spectrum agents, is done in an early and empirical fashion (Klein Klouwenberg et al. 2015). However, administration of unnecessary antibiotics will develop bacterial resistance against these drugs.

Currently, the most important aspect to improve outcome is early recognition of infection and prompt initiation of appropriate empiric antibiotic treatment. Initiation too late or inappropriate antibiotic therapy is associated with adverse outcomes (Ferrer et al. 2014). In addition there is an unmet need for data regarding when to stop antibiotics in two particular clinical scenarios:

- It is not clear which is the best time point to reassess a patient in order to define if an infectious process is present.
- To define when the patient is not responding to the antibiotic being administered without reaching clinical stability or, oppositely, to define when infection is clinically cured and antibiotics could be stopped.

A biomarker or biological marker generally refers to a measurable indicator of some biological state or condition (Martin-Loeches et al. 2015). In the context of infection, the ideal biological marker would discriminate when a patient needs to discontinue or de-escalate an antibiotic course.

Evidence Against

It is now clear that at least for patients with severe infections the timing of antibiotic onset is markedly associated with the outcome (Kumar et al. 2006; Ferrer et al. 2014). However, data concerning the ideal duration of antibiotic therapy is scarce, even though growing evidence from recent studies suggests that short courses of treatment are effective and safe. Interestingly, most of these studies did not use biomarker-guided protocols to reduce antibiotic use.

Two landmark studies specifically evaluated the impact of fixed durations of antibiotic therapy to treat severe infections in intensive care unit (ICU) patients (Chastre et al. 2003; Micek et al. 2004). The PneumA trial (Chastre et al. 2003) was a prospective randomised controlled trial (RCT) in 51 French ICUs, designed to assess whether 8 days was as effective as 15 days of antibiotic therapy in microbiologically documented late-onset ventilator-associated pneumonia (VAP) (n=402). No difference in the all-cause mortality rate was observed between the two groups (18.8% vs. 17.2%). In the subgroup of patients with VAP caused by non-fermentative Gram-negative bacilli, patients treated for 8 days had higher rates of recurrence of infection as compared to the longer treatment group (40.6% vs. 25.4%, $p<0.05$), but with no excess of mortality (23.4% vs. 30.2%, p=NS). In addition, the rate of emergence of multidrug-resistant bacteria was significantly lower in the 8-day therapy group (41.2% vs. 62.3%, p=0.04).

The second study (Micek et al. 2004) was a single-centre prospective RCT designed to evaluate the effectiveness and safety of an active discontinuation policy for the duration of antibiotic therapy for VAP (n=290). The active discontinuation policy consisted of a) initial administration of adequate antibiotic treatment and b) antibiotics should be discontinued if b.1) the infiltrates were considered to be non-

infectious aetiology or b.2) the signs and symptoms suggested that the active infection had resolved. The authors showed that the active discontinuation policy could safely decrease the duration of antibiotic therapy to 6 days in comparison to the standard of care, which was 8 days (p=0.001). Both groups presented comparable clinical outcomes, namely: hospital mortality, ICU and hospital length of stay (LOS) (p=0.357, p=0.798, p=0.865, respectively). In addition, the rate of VAP recurrence was similar in both groups (p=0.667).

Similar data have been published in other relevant clinical situations, such as community-acquired pneumonia and non-complicated pyelonephritis (Li et al. 2007; Sandberg et al. 2012). Additional benefits demonstrated by these studies were lower emergence of bacterial resistance, better adherence to treatment, decreased toxicity and reduced costs.

A randomised controlled trial (RCT) on non-critically ill patients with complicated intra-abdominal infections demonstrated that, in patients with adequately controlled infections, a fixed short course of antibiotics (median duration of 4 days) produced similar outcomes, namely rate of septic complications, as compared to 10 days of therapy (Sawyer et al. 2015).

Taken together, these findings all suggest that, even in ICU patients with severe infections, namely VAP and intra-abdominal infection, the duration of antibiotic therapy can be safely shortened to 6-8 days, regardless of the use of biomarkers.

> "the ideal biological marker would discriminate when a patient needs to discontinue or de-escalate an antibiotic course"

Evidence in Favour

As far as we are aware there are 11 RCTs of procalcitonin (PCT)-guided antibiotic therapy in critically ill patients for initiation and cessation of antibiotic therapy or both (Svoboda et al. 2007; Nobre et al. 2008; Schroeder et al. 2009; Stolz et al. 2009; Hochreiter et al. 2009; Bouadma et al. 2010; Jensen et al. 2011; Layios et al. 2012; Deliberato et al. 2013; Annane et al. 2013; Shehabi et al. 2014). The relative quality of the majority of these RCTs has been discussed in detail elsewhere (Póvoa and Salluh 2012).

Despite its limitations, these trials make PCT the most studied biomarker to guide antibiotic therapy in critically ill patients (**Table 1**). Concerning the decision to start antibiotics (Svoboda et al. 2007; Bouadma et al. 2010; Jensen et al. 2011; Layios et al. 2012; Annane et al. 2013), not a single trial was able to demonstrate that PCT-guided initiation of antibiotic therapy constitutes a helpful strategy in comparison to current clinical judgment for decreasing antibiotic consumption in critically ill patients. This could be related to the fact that clinicians already have a low threshold to start antibiotics and that, at least in critically ill patients, biomarkers are unlikely to favourably change that threshold.

On the contrary, with the exception of two RCTs (Jensen et al. 2011; Annane et al. 2013), all the other PCT-guided antibiotic

1. Soni N.J. et al., J Hosp Med 2013;8 (9): 530-40. 2. Meisner, M., Procalcitonin – Biochemistry and Clinical Diagnosis, UNI-MED (Bremen) 2010; ISBN 978-3-8374-1241-3.

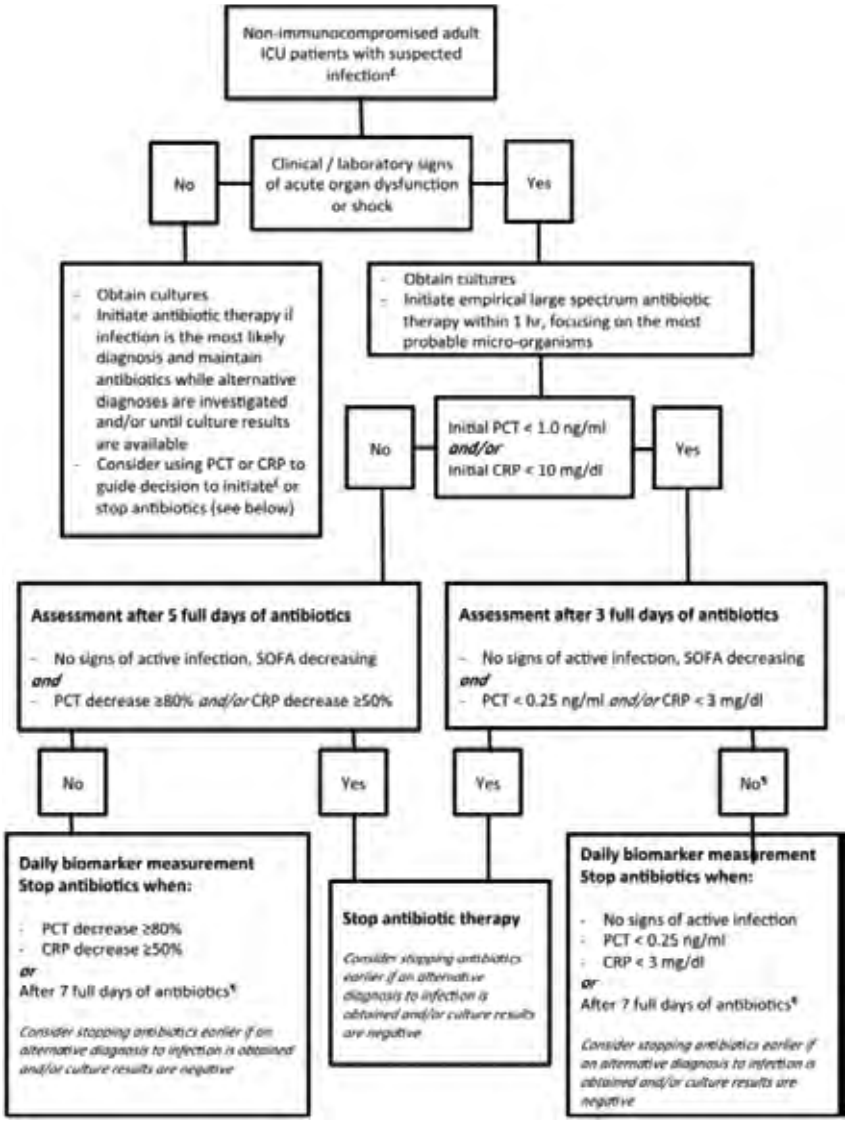

Figure 1. Integrative Algorithm for C-Reactive protein (CRP) or Procalcitonin (PCT)-Guided Antibiotic Therapy In Critically Ill Patients[§]

SOFA Sequential Organ Failure Assessment (Modified from Salluh et al. 2014)

[§] This flowchart does not apply to immunocompromised patients (example: those with febrile neutropaenia) or to patients with infections requiring long-term antibiotic therapy (example: infectious endocarditis, osteoarticular infections, cerebral abscess). C-reactive protein (CRP) was tested only in a single-centre trial with predominantly medical intensive care unit patients (Oliveira et al. 2013). Even for procalcitonin (PCT), one must be careful in cases of recent (i.e., less than 4-5 days) surgical or non-surgical trauma, because of the potential influence of these conditions on PCT levels.

[£] Most trials investigating PCT-guided protocols tested the role of this marker in guiding the decision on antibiotic cessation (**Table 1**). Initiating antibiotics for all critically ill patients with suspected infection is probably the safest decision, regardless of the levels of laboratory biomarkers. However, this decision must be reassessed daily taking into account the patient clinical course. According to a Danish multicentre trial, PCT-guided antibiotic escalation cannot be recommended, since this strategy resulted in higher consumption of broad spectrum antibiotics, longer duration of antibiotic therapy and longer stay in the intensive care unit, without improving survival (Jensen et al. 2011).

[¶] Consider stopping antibiotics before day 7 of antibiotic therapy in patients with no proven infection (i.e., negative cultures) regardless of the levels of C-reactive protein (CRP) or procalcitonin (PCT) (Oliveira et al. 2013).

stewardship trials showed that using very similar PCT-algorithms was associated with a shorter duration of antibiotic therapy. Of note, this reduction was achieved with no apparent harm; i.e., there were comparable ICU LOS, relapse/recurrence rates of infection as well as mortality rate between patients of the PCT-guided group and controls (**Table 1**).

In a recent meta-analysis (Schuetz et al. 2012) it was clear that for ventilator-associated pneumonia (VAP), use of PCT-guided algorithms allowed a reduction of 3 days (from 14 to 11 days) in the mean duration of antibiotic therapy. However, in some trials the shortening of the antibiotic therapy courses was achieved due to excessively long and fixed antibiotic treatments in the control groups (Póvoa and Salluh 2012). This strategy, i.e., fixed and long courses of antibiotics in the control groups, may have led to an 'artificial' reduction of antibiotic treatment in the PCT-based arms. In addition, these trial designs also did not take into account data available for more than a decade from trials showing that a 6 to 8-day course of antibiotics is effective and safe to treat severe infections (Chastre et al. 2003; Micek et al. 2004).

How Can we Properly Use Biomarkers?

With the previously mentioned limitations in mind, we should ask: how can we properly use biomarkers such as PCT and C-reactive protein (CRP) to guide antimicrobial therapy (initiation and duration) in severe sepsis? (Vincent and Teixeira 2014). First, we believe that future clinical RCTs should use less strict entry criteria that would better reflect our real-life ICU patients with sepsis. Second, a great deal of effort must be put into conducting multicentre studies, involving a large number of patients, ideally in different regions of the world. Lastly, biomarker-guided strategies must be tested against a comparator that actually reflects the "best care" (i.e., implementation of the best available evidence), which increasingly balances toward shorter courses of antibiotic therapy instead of the highly variable, and usually longer than necessary, "standard care". In our opinion, it means comparing PCT-algorithms with control treatment in which the maximum duration of antibiotic therapy is set up in 7-8 days (Chastre et al. 2003; Micek et al. 2004). Until these studies are performed and their results become available, clinicians should perhaps use a "double-trigger" strategy as proposed by Oliveira et al. (2013). In this

Table 1. Principal Characteristics of the Randomised Controlled Trials Assessing the Role of Procalcitonin (PCT)-Guided Antibiotic Stewardship in Adult Critically Ill Patients

	Trial	Sample size, n (PCT/control)	Rate of exclusion, n(%)	Setting	Infections Community/ nosocomial, n/n	Pneumonia, n	PCT assay	Minimum duration AB therapy	Decision to start antibiotics (no Atb), PCT/control	Duration of antibiotic therapy, PCT/control, days	Overruling PCT algorithm, %
Svoboda 2007		72 (38/34)	381 (84)	SICU	0/72	NA	PCT-Q			9 / 13	29%
Nobre 2008	ProSEP	79 (39/40)	203 (72)	Mixed ICU	53/26	52	TRACE			8(4-27)/14(6-39)	19%
Schroeder 2009		27 (14/13)	98 (78)	SICU	0/27	8	PCT LIA	yes		6.6±1.1/8.3±0.7	
Stolz 2009	ProVAP	101 (51/50)	63 (38)	Mixed ICU	0/101	101	TRACE	yes		10(6-16)/15(10-23)	16%
Hochreiter 2009	ProSICU	110 (57/53)	285 (72)	SICU	0/110	43	PCT LIA			5.9±1.7/7.9±0.5	
Bouadma 2010	PRORATA	601 (307/314)	685 (52)	Mixed ICU	326/275	394	TRACE	yes	4(1.7%)/15(4.8%)	10.3±7.7/13.3±7.6	53%
Jensen 2011	PASS	1200 (604/596)	3 (0.3)	Mixed ICU	480/720	666	TRACE		56 (17.9%)/37 (17.6%)	6(3-11)/4(3-10)	17.9%
Layios 2012		509* (258/251)	0	Mixed ICU	323/344	419	TRACE		26(7.6%)/21(6.7%)	DDD (ICU days) 147/100/141/100	34.6%
Deliberato 2012		81 (42/39)	184 (69)	Mixed ICU		14	PCT-LIA	yes		10(3-39)/11(2-45)	29%
Annane 2013		58 (30/28)	1158 (92)	Mixed ICU	36/22		TRACE		4 (15%)/4(15%)	5(2-5)/5(3-5)	19%-37%
Shehabi 2014	ProGUARD	392 (196/196)	1197 (76%)	Mixed ICU		170	TRACE			9(11-22)/11(6-22)	3%

Results are expressed as mean ± standard deviation or median (interquartile range)
ATB antibiotic ICU intensive care unit LOS length of stay PCT procalcitonin SICU Surgical intensive care unit TRACE time-resolved amplified cryptate emission
*Layios (Layios et al. 2012) – episodes per patient; 1.4±1.1 in PCT group and 1.2±1.0 in controls

	Trial	LOS ICU, PCT/control, days	Superinfection, PCT/control, n(%)	Relapse, PCT/control, N(%)	Mortality 28d, PCT/control, n(%)	Mortality 60d, PCT/control, n(%)
Svoboda 2007		16.1±6.9/19.4±8.9			10/38 (26%)/13/34 (38%)	
Nobre 2008	ProSEP	4(1-21)/7(1-91)	7/31 (22.5%)/ 11/37 (29.7%)	1/39 (2.6%)/1/40 (2.5%)	8/39 (20.5%)/8/40 (20%)	
Schroeder 2009		16.4±8.3/16.7±5.6			3/14 (21.4%)/3/13 (23.1%)	
Stolz 2009	ProVAP	13(7-21)/13.5(8-22.2)	7/51 (13.7%)/ 6/50 (12%)		8/51 (16%)/12/50 (24%)	
Hochreiter 2009	ProSICU	15.5±12.5/17.7±10.1			15/57 (26.3%)/14/53 (26.4%)	
Bouadma 2010	PRORATA	15.9±16.1/14.4±14.1	106/307 (34.5%)/ 97/314 (30.9%)	20/307 (6.5%)/16/314 (5.1%)	65/307 (21.2%)/ 64/314 (20.4%)	92/307 (30%)/ 82/314(26.1%)
Jensen 2011	PASS	6 (3–12)/5 (3–11)			190/604 (31.5%)/191/596 (32%)	231/604 (38.2%)/ 220/596 (36.9%)
Layios 2012		7(4-16)/7(4-18)			56/258 (21.7%)/53/251 (21.1%)	
Deliberato 2012		3.5(1-57)/3(1-28)	2/18 (11%)/3/19 (16%)	2(4.8%)/1(2.6%)	2(2.4%)/4(10.3%)	
Annane 2013		22(8-42)/23(10-60)	6/174 (3%)/12/183(12%)		7/31 (23%)/10/30 (33%)	
Shehabi 2014	ProGUARD	6(3-9.5)/6(4-10)			21/196 (11%)/15/198(8%)	35/196 (18%)/31/198 (16%)

Some results are expressed as mean ± standard deviation or median (interquartile range)

RCT, in which a PCT-guided protocol was compared to a CRP-guided strategy, antibiotics were stopped according to clinical response to therapy associated with either a pre-established reduction in the circulating levels of these biomarkers or the completion of 7 full days of treatment, whichever comes first. In this single-centre study that evaluated patients with severe sepsis and septic shock, PCT and CRP were similarly effective in ensuring an early interruption of antibiotics [7(6-8.5) vs. 6(5-7) days, respectively].

Proposal of an Integrative Algorithm

Considering the critical revision of present data, we propose an integrative algorithm, incorporating the available evidence on using PCT or CRP-guided strategies, in addition to clinical and laboratory information, to reduce antibiotic therapy in critically ill patients. Our proposal is presented in **Figure 1** (Salluh et al. 2014). It must be stressed that biomarkers represent only one of the available tools to promote antibiotic stewardship and should never be used as a single tool. Additional measures to reduce inappropriate antibiotic exposure should always be considered.

Conclusion

Different strategies have been designed to implement and operationalise antibiotic stewardship in critically ill patients. Antibiotics are very powerful drugs, that when adequately and used in a timely manner make a huge difference in the prognosis of severe sepsis and septic shock patients. Antibiotics only treat infections, not sepsis-like syndromes. But it is also important to recognise that antibiotics are not innocent players; their use, in particular if prolonged and inadequate, is associated with increased duration of mechanical ventilation, LOS, mortality, recurrence of infection, toxicity, emergence of bacterial resistance and costs.

> **"Biomarker-guided strategies must be tested against a comparator that actually reflects the "best care"**

To approach this complex problem we need new approaches and helpful tools. A strategy like the one we propose, although not validated, puts together valuable and reliable information from different RCTs. This algorithm takes into consideration a "double-trigger" strategy (time/clinic course and biomarker level) and could be implemented as a helpful tool in the daily clinical decision making process at the bedside.

Conflict of Interest

Pedro Póvoa has unrestricted research grants from ThermoFisher Scientific and Virogates. The other authors state that they have no competing interest with the subject. ■

Abbreviations

CRP C-reactive protein
LOS Length of stay
PCT Procalcitonin
RCT Randomised controlled trial

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MEDICATION SAFETY

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All drugs are inherently dangerous. In critical care we give large numbers of particularly dangerous drugs to very sick people, who have little physiological reserve to cope with additional problems. When patients are admitted to or transferred out of critical care we have to transfer complex information about patients' medications. The staff prescribing and administering medications are often inexperienced and working as part of a team that is attempting to communicate information in difficult circumstances. Staff are also dependent on elaborate and sophisticated technology to 'help' them in this process. The complexities of the medication process have also produced some confusing terminology, which is defined in **Table 1**. Faced with these problems we have to do all that we can to minimise the risks associated with medications. We will never make medications completely safe. Medication safety is a continuous process of improvement and learning.

Strategies to Reduce Risk

Improving medication safety has been the subject of considerable research and investment. Before describing the details of specific actions it is important to note that the general safety culture of a unit will strongly influence patient safety within the unit (Kho et al. 2005). This culture is dependent on the quality of management in the unit (Morello et al. 2013). Getting management right will be essential in promoting medication safety. There should also be a structured review of all the medications on each consultant ward round, as all medications are potentially dangerous. Structured rounds (Lane et al. 2013) and clear ward round goal setting (Pronovost et al. 2003) are essential preconditions for medication safety.

The effectiveness of specific interventions (**Figure 1**) to improve medication safety has been well reviewed in a recent meta-analysis (Manias et al. 2012). The following interventions have been shown to improve safety:

Involvement of a Pharmacist: The recent core standards issued by the UK Faculty of Intensive Care Medicine (Core Standards Working Party of the Joint Professional Standards Committee 2013) recommend that all critical care units have a competent clinical pharmacist, who will attend consultant ward rounds and be an integrated part of the critical care team. This recommendation is based on evidence (Preslaski et al. 2013; MacLaren et al. 2008). The pharmacist role is relatively new in critical care, and encouraging pharmacists to be fully engaged in ward rounds (Leape et al. 1999) and teaching may be a challenge. A review of the role of the critical care pharmacist stresses the cost saving implications as well as the clinical benefits (Weber et al. 2003).

> **Medication safety is a continuous process of improvement and learning**

Medicines Reconciliation: Not only are drugs dangerous, but also stopping them precipitously can be harmful, for example beta blockers (Shammash et al. 2001) and statins (Tziomalos et al. 2008). One of the most common prescribing errors identified in a review of patient safety incidents was to prescribe a drug to which the patient was known to be allergic (Thomas and Taylor 2014). Obtaining a drug history in a comatose patient may be challenging, and ensuring all patients have a medicines reconciliation is an organisational challenge. The reconciliation process should be repeated at transfer from critical care; otherwise patients may continue to receive drugs that were only appropriate for the critical care episode (examples reported as patient safety incidents include proton pump inhibitors, clonidine and steroids). There may also be problems with drugs that have complex dosing protocols, for example insulin, gentamycin and vancomycin. These problems can be controlled by structured handovers at all transfers of care (Segall et al. 2012; Pickering et al. 2009).

Education of Staff: Educational theory is clearly outside the scope of this review, but it should be carefully considered before introducing any educational intervention. Interventions that offer specific feedback to individual prescribers reduce prescribing errors (Thomas et al. 2008), and interventions in the workplace are more effective than didactic lectures (Ford et al. 2010). In Greater Manchester we have introduced a multifaceted educational and audit-based programme to reduce the number of prescriptions of medications to which the patient is known to be intolerant to (Greater Manchester Critical Care & Major Trauma Services Network 2015) (**Figure 2**). Some education can be delivered using e-learning, which removes the immediate requirement for an educator and allows monitoring of the resource usage (Thomas 2013; Thomas 2012). The costs of basic provision of e-learning should be affordable for units willing to invest in the material, but this should be an adjuvant to workplace learning, which does require staff to deliver and receive the training.

Technological Interventions

There are a number of technological interventions that have not shown a reduction in patient safety incidents associated with their introduction (Manias et al. 2012). Failure to show an improvement in patient safety with these interventions may reflect problems with study design, as the interventions were generally studied within weeks or months after introduction. This time period would not allow units to deal with teething problems associated with introducing

complex technology. Studies also frequently do not describe the complex processes in a unit that should be associated with the introduction of new technology. For example, a study showing lack of benefit with smart pump technology did not use the drug libraries available in the pumps (Rothschild et al 2005). There are also problems with producing interventional studies that are adequately powered to detect reduction in harm when the harm is relatively uncommon (Black 1996).

Examples of technological innovations that have not been proven to improve medication safety include:

Electronic prescribing: Electronic prescribing removes many prescribing errors connected with poor handwriting, lost charts and dosing errors, but it allows other errors. Review of patient safety incidents (Thomas and Taylor 2014) suggests the most common problems are associated with the transfer of drug information where a unit uses a different system to the rest of the hospital. Incidents also clearly increase in the time that a new system is introduced, and the introduction of electronic prescribing should be properly supported. There are also ongoing issues with medications discontinuing at their stop dates without being reviewed and drugs remaining on the system after they are no longer required.

Smart pump technology: Pumps that have libraries of drugs that then limit the potential rates of infusion to safe levels, clearly display the drug being infused, and use specific barcoding of syringes so that only the correct drug can be infused, should on face value improve medication safety. Unfortunately there is a lack of evidence for the effectiveness of these interventions (Manias et al. 2012). This lack of evidence may be because, in some studies evaluating this technology, the technology was not actually being used as it should have been (Rothschild et al. 2005). The methods used to introduce this technology are also complex and involve training large numbers of staff. Patient harm associated with mis-setting of pumps is very important for a few patients, but it is difficult to detect a change in the rates of these uncommon events with randomised trials. Regardless of the evidence of benefit, it is clear that manufacturers are going to continue to develop this technology. When choosing this technology it is essential to consider the ergonomic design of the pump to check that staff are going to be able to understand how to use it. It would also be helpful to be able to assess a pump being used in another unit before deciding to purchase it. It is also important to clearly define the assistance the supplier will provide in training and to define how you will introduce the new technology safely.

Table 1. Terminology

Adverse drug events (or adverse drug reactions): events that describe harm suffered by patients as a result of medication use; the harm may be unavoidable. There is often considerable uncertainty about the relationship between an adverse event and a particular drug, and there are tools to assess the probability that the drug and the event are linked (Meyboom et al. 1997). This uncertainty may result in us underestimating the harm associated with medication use.

Medication errors: avoidable actions by staff, which may or may not result in patient harm.

Patient safety incidents (or 'critical' incidents): episodes of harm or potential harm that are self-reported by staff and may or may not have been the result of an 'error'. Patient safety incidents rely on the voluntary reporting of incidents; many incidents may go unreported.

Global triggers: adverse events that should prompt a review of medications to see if medication use could have been associated with the adverse event. For example, a very abnormal prothrombin result should be reviewed for potential errors in the prescription or administration of warfarin (Griffin and Resar 2007). Global triggers do not rely on voluntary reporting, but will not capture the broad scope of patient safety incidents. Therefore global triggers and incident reporting should be used together (Stockwell and Kane-Gill 2010).

High-risk medications: medications that are commonly associated with patient harm (Institute for Healthcare Improvement 2012). High-risk medications that we should pay particular attention to are insulins, anticoagulants, inotropes, opiates and variable dose antibiotics (for example gentamycin and vancomycin). There is specific guidance around the use of these medications. Training and decision support and protocols of care should first be focused on these drugs.

Figure 1. Strategies to Improve Medication Safety on Critical Care

Causes for Adverse Drug Events

We have reviewed patient safety incidents reported from most critical care units across the North West of England since 2009, described the broad classification of these incidents (Thomas and Taylor 2012), and reviewed

Figure 2. Part of the Greater Manchester Critical Care Network Educational Programme

incidents specifically associated with medications (Thomas and Taylor 2014). These reviews have shown that medication incidents represent the largest number of incidents that are clearly preventable, and that incidents that are preventable are as likely to be associated with harm as other incidents. The reviews also suggested that the rate of reporting of medication incidents per thousand patient days was ten times higher in some units than other units. This variation seemed to be independent of the type of unit or the network in the North West; significant variation without a clear explanation suggests that there is scope for quality improvement in many units (Tomson and van der Veer 2013). Most incidents associated with patient harm result from problems with the prescription or administration of medicines. With respect to prescription problems the most common problems were not prescribing medications that were indicated, not prescribing according to the British National Formulary and not prescribing according to unit protocols. This suggests that providing drug information to prescribers and improving the provision of information about drugs, particularly information about local protocols, would improve medication safety. The use of forcing functions, for example standard prescriptions, would presumably also help compliance with local protocols. With respect to administration, most common problems were associated with the incorrect checking of medications. This may in part because the role of the second checker has not always been clearly defined; without this definition the second checker could result only in causing the first checker to stop concentrating on the checking process (Armitage 2008).

The drugs most commonly involved were drugs already described as high-risk medications, so confirming that efforts to improve medication safety should concentrate on these drugs. With insulin the most common cause of hypoglycaemia was a failure to adjust the insulin infusion rate or provide alternative calories when enteral feed was interrupted (Thomas and Taylor 2014). Incorrect selection of arterial flush solutions with the potential for inaccurate measurement of blood glucose (Leslie et al. 2013) continued to be reported into 2014.

In summary medications are dangerous and should be stopped as soon as they are no longer needed. Reducing harm from medications requires units to develop a safety culture that encourages continual learning from episodes of harm. Improvement requires investment in systems of care and consistent ways of working. The engagement of pharmacists in this process is critical and is more evidence-based than investment in expensive technology. ■

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FRAILTY IN THE CRITICALLY ILL PATIENT

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This review explores current definitions of frailty, methods available to diagnose it, and its application to perioperative and critically ill patients.

Frailty is increasingly recognised as a potential contributor to patient outcome during an episode of critical illness. However, there is currently no consensus definition or assessment tool. Two main models exist to conceptualise frailty —the "frailty phenotype" and the "deficit model". Both models have been validated in the community setting to be predictive of patient outcomes. However, they are limited in critical care by their applicability at the bedside. In the community, a diagnosis of frailty is associated with increased risk of falls, hospitalisation, institutionalisation and death. The direct pathophysiological pathway that results in a frail state is currently unknown, despite considerable research in this area. Frail patients have disordered homeostasis of many systems, including the inflammatory, coagulation, and neuro-endocrinal systems. The prevalence of frailty is approximately 1 in 5 elderly patients, and is increased in patients undergoing major surgery. Frail surgical patients are at higher risk of morbidity and mortality than non-frail patients. The role of frailty in the critical care environment is less clear. Thus far, the small number of studies has produced conflicting results. It appears that frailty has a higher prevalence than in the community and may be associated with poorer ICU outcomes. However, further research into the application of frailty assessment tools in the ICU is required.

Recently there has been increased recognition of the importance of functional status for patient outcome following Intensive Care Unit (ICU) admission. This includes patient functional status both upon ICU admission and discharge. Similarly, frailty is one determinant of a patient's functional state and its impact upon outcomes is being increasingly recognised (McDermid et al. 2011; McDermid and Bagshaw 2014). Previous literature on this topic has focused on geriatric and perioperative patients, in whom frailty has been shown to be associated with an increased risk of hospital admission, institutionalisation, postoperative complications and mortality (Song et al. 2010; Graham et al. 2009; Fried et al. 2001; Woods et al. 2005; Rockwood et al. 2005; Xue 2011; Partridge et al. 2012). However, the lack of a consensus definition and uncertainty on how to best assess frailty have resulted in limited research in the critically ill. There is increasing evidence suggesting that the consideration of frailty in critically ill patients may provide additional prognostic information.

What is Frailty?

There is currently no consensus definition of frailty nor a single definitive assessment tool, despite recent international attempts at consensus (Fried et al. 2001; Xue 2011). However, frailty is commonly conceptualised as a " multidimensional geriatric syndrome characterised by an increased vulnerability, resulting from an age-associated decline in reserve and function, such that the ability to cope with everyday or acute stressors is compromised" (Xue 2011). The precise pathophysiology of frailty is incompletely understood. Frailty appears to be differentiated from normal ageing by the accumulation of multiple pathological abnormalities that contribute to frailty's characteristic clinical manifestations of sarcopenia, malnutrition, and decreased energy expenditure (Hubbard and Woodhouse 2010) (**Figure 1**).

The primary pathological process has been postulated to be chronic inflammation (Hubbard and Woodhouse 2010). Other significant pathological contributors are likely to include disordered coagulation, as well as dysfunction of the immune and neuro-endocrinal systems (Hubbard et al. 2009a; Waltson et al. 2002; Hunt et al. 2010). These suppositions are supported by research revealing that frail patients have significantly altered levels of C-reactive protein, interleukin-6, tumour necrosis-factor, as well as elevated clotting factor VIII, fibrinogen and D-dimer levels. Additionally, frail patients are more likely to have a disordered hypothalamic-pituitary axis, disordered glucose metabolism and lower vitamin D levels (Hunt et al. 2010; Bayliss et al. 2013; Ensrud et al. 2011; Leng et al. 2004).

How these biological abnormalities contribute to frailty is also poorly understood. It is known that there exists a strong association between chronically elevated inflammatory cytokines and decreased physical performance, muscle weakness, atrophy, and the progression of disability in elderly patients (Cesari et al. 2004; Ferruci et al. 1999). However, elderly patients often have altered biochemical markers as a result of other concurrent chronic illnesses such as renal failure and cardiovascular disease (Waltson et al. 2002). Thus it appears that a critical mass of abnormalities in a patient's homeostatic systems is required before a frail state develops (Hubbard and Woodhouse 2010). Further confounding current pathophysiological models is the find-

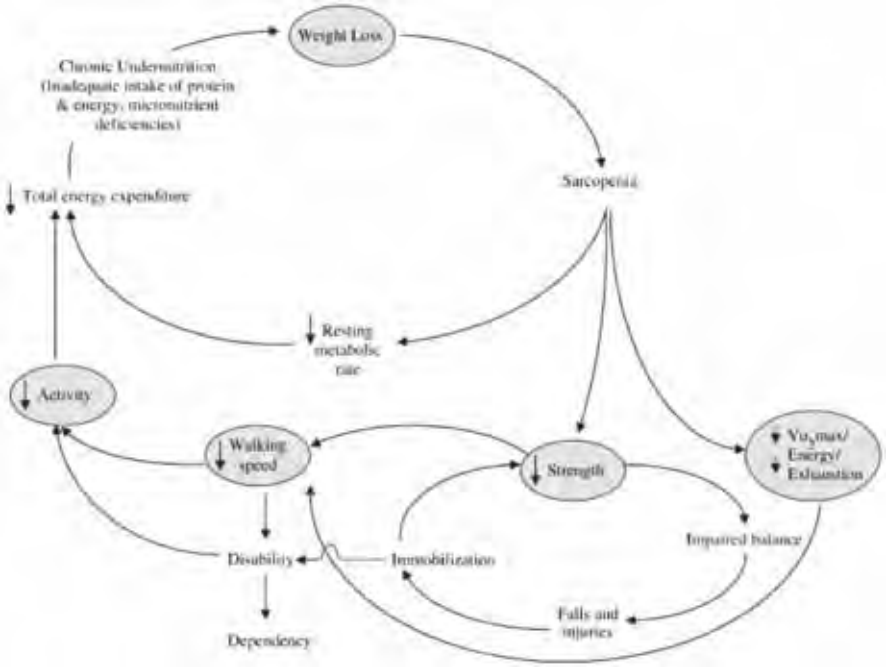

Figure 1. Cycle of Frailty
The cycle of frailty as evident by decreased energy expenditure, deconditioning and subsequent complications. (Reproduced with permission)
Source: Fried and Walston (1998)

ing that these observed biological abnormalities might not entirely account for the pathology underlying a frail state. The psychosocial environment of a patient may also impact on the genesis of frailty. This is supported by research demonstrating frailty's association with smoking, lower socio-economic status and lack of physical exercise (Hubbard et al. 2009b; Lang et al. 2009).

How to Diagnose and Measure Frailty

To date, several methods have been developed to diagnose and measure frailty (Whitson et al. 2007). A recent review identified 27 published tools for the assessment of frailty that range from isolated biochemical abnormalities or physiological parameters to detailed multidisciplinary team assessments (Bouillon et al. 2013; Sternberg et al. 2011). However, frailty research and debate is driven by two distinct but validated frailty models. The first model views frailty as a physical syndrome or 'phenotype'. The second model views frailty as a collection of deficits in measurable health domains, (the 'deficit' model) (Sternberg et al. 2011). A recent review revealed that 83% of published literature on frailty used either of these models (Bouillon et al. 2013).

Phenotype Model

The phenotype model is based on the pioneering work of Fried et al. in North America. Fried et al. followed more than 5300 elderly patients for seven years, and found the presence of greater than three of the following features: unintentional weight loss, weakness, low energy levels, slowness, and decreased physical activity characterised a frail state (Fried et al. 2001). In this study a frail state was predictive of falls, hospitalisation, and death with adjusted hazard ratios of 1.29 (CI 1-1.68), 1.29 (CI 1.09-1.54), and 2.24 (CI 1.51-3.33) at 3 years respectively. This was the first study to show that, although age and co-morbidity were associated with frailty, they did not define frailty itself and frailty exists as a distinct clinical entity. Additionally this study was the first to assess patients in the community, as opposed to patients already admitted to hospital or other healthcare institutions.

Frailty Model

The alternative approach considers frailty as the accumulation of numerous health deficits. The greater the number of deficits a patient acquires, the higher risk of a frail state (Mitnitski et al. 2001; Rockwood and Mitnitski 2011). The Canadian Health Study of Aging is the largest study utilising this approach. This study looked at over 10,000 elderly patients, and after integrating patient co-morbidities, clinical examinations findings and an assessment of activities of daily living, developed a 70-point frailty index. The frailty index was shown to be predictive of death and institutionalisation at 70 months, with hazard ratios of 1.26 (CI 1.24–1.29) and 1.56 (CI 1.48–1.65), respectively (Rockwood et al. 2007). It may be contended that the frailty index approach is consistent with the concept that development of frailty is a gradual process rather than an absent or present phenomenon. Rockwood et al. have suggested that the frailty index may be a more robust and sensitive measure of frailty-associated outcomes than the frailty phenotype (Rockwood et al. 2007). However, Bouillon et al. have suggested that the two models of frailty have similar predictive and discriminative ability to detect frailty (Bouillon et al. 2013).

Limitations

A major limitation of many frailty assessment tools is their impracticality in many clinical contexts. Many tools are not suitable for use at the bedside, time-consuming to perform, require specially trained clinicians, or the performance of specialised biochemical and physical investigations.

Tools

Newer tools have been developed that may overcome some of these barriers and increase their practicality, especially in critical care.

- **Clinical Frailty Scale:** The Clinical Frailty Scale (CFS) has been derived from the frailty index developed in the Canadian Health Study of Aging. The CFS is a simple visual analogue 9-point scale ranging from very fit (1) to terminally ill (9), with a score greater than 4 indicating frailty (**Figure 2**). In a cohort of over 2,300 patients, the CFS was shown to be predictive of six-month mortality and institutionalisation, with hazard ratios of 1.30 (CI 1.27–1.33) and 1.46 (CI 1.39–1.53) respectively. Furthermore, it has been validated against the frailty index showing a high degree of correlation, with a Pearson correlation coefficient of 0.80, $p < 0.01$ (Rockwood et al. 2005). The greatest benefit of the CFS is its ease of use, lack of required ancillary testing, and its ability to be applied at the bedside.
- **Edmonton Frailty Scale:** Another simple but validated tool is the Edmonton Frailty Scale (EFS). The EFS incorporates a brief 10-point assessment of specific health domains, including cognition, medication usage, nutrition and social supports. Functional status is assessed via the 'timed up and go' or TUG test. The EFS has been validated for use by primary care physicians and geriatricians (Hilmer et al. 2009), and also has been shown to be predictive of outcome in acute general medical in-patients and patients

admitted with acute coronary syndromes (Hilmer et al. 2009; Graham et al. 2013). Rolfson et al. (2006) demonstrated the ease of EFS usage in 158 elderly patients. Using a non-medical assessor and a trained geriatrician to assess frailty, Rolfson et al. found a high level of agreement between the EFS values obtained by both assessors (Pearson correlation coefficient 0.64, $p < 0.01$) and importantly that the EFS took less than 5 minutes to administer (Rolfson et al. 2006). Although a simple and validated tool, the EFS is potentially limited in its assessment in the critically ill by the need for a practical functional assessment.

Tool Comparison

To date, there has been limited comparison between the different frailty tools to predict patient outcomes. A systematic review by De Vries et al. concluded that whilst many tools have construct validity, comparisons between them are limited and difficult due to the range of population groups assessed. The various combinations of clinical and investigation parameters used further limit comparison (de Vries et al. 2011). A 2008 editorial contended that different tools to assess frailty may be required in different situations and no one tool may be ideal, e.g. bedside clinician versus public health officers seeking to explore population-based trends and planning requirements (Martin and Brighton 2008).

Frailty in the Community

The prevalence of frailty in the community has been reported to be between 6.9% to 22.7%, depending on the population studied and the tool used (Collard et al. 2012). Frailty has been consistently shown to have a higher prevalence in women and increasing prevalence with advancing age (Song et al. 2010; Graham et al. 2009; Woods et al. 2005; Collard et al. 2012). Furthermore, it appears that it is more common in Southern Europe and South America, perhaps reflecting cultural differences in diagnosing frailty in these respective populations (Santos-Eggimann et al. 2009; Alvarado et al. 2008).

Frailty in the Perioperative Setting

Frailty is a significant predictor of outcome in elderly patients presenting for surgery, regardless of the frailty assessment tools employed (Partridge et al. 2012). The reported prevalence of perioperative frailty varies markedly between 4-50% (Makary et al. 2010; Sepeheri et al. 2014), but is generally higher than that in community-based studies, irrespective of the surgery type. This may be influenced by the underlying indication for surgery, as the common surgical indications of cardiovascular or malignant diseases are also associated with a frail state.

Figure 2. The Dalhousie Clinical Frailty Scale
Source: geriatricresearch.medicine.dal.ca/pdf/Clinical%20Faily%20Scale.pdf

Current evidence suggests that frailty is associated with significant postoperative complications. In mixed general, vascular and orthopaedic surgical populations frailty has been associated with increased delirium, infection, thromboembolic disease and pressures areas (Partridge et al. 2012). It has also been associated with prolonged hospital length of stay and an increased risk of institutionalisation post discharge (Partridge et al. 2012). One study reported that one-third of patients aged >65 years assessed as frail pre-operatively were institutionalised at 6 months post major elective surgery (Robinson et al. 2011).

Frailty has a potentially significant influence upon outcomes in the cardiac surgery and transplantation populations. Frailty, assessed in a variety of ways and as a component of a comprehensive perioperative assessment, has been shown to be associated with increased morbidity and mortality following cardiac surgery (Sepeheri et al. 2014; Afilalo et al. 2010; Lee et al. 2010; Sundermann et al. 2011). One study revealed that frailty was a more reliable predictor of one- and twelve-month mortality when compared to the more commonly administered EuroScore (Sundermann et al. 2011). In addition, the Fried frailty phenotype has been shown to be a better predictor of both quality of life and mortality in liver transplantation candidates than the traditional Model for End-Stage Liver Disease (MELD) score (Derck et al. 2015; Lai et al. 2014). The high prevalence of frailty in perioperative patients and its association with adverse postoperative outcomes may offer a unique opportunity for multidisciplinary-focused patient assessment and postoperative planning.

Frailty and Critical Care

Frailty is increasingly recognised as a potential contributor to critically ill patient outcome. However, research has been limited by difficulty using frailty diagnostic tools, due to a lack of premorbid history, the presence of interceding acute critical illness and the impracticality of applying many of the tools at the bedside. Thus, existing evidence of the utility of frailty assessment in critically ill patients is derived from a relatively small number of studies (**Table 1**). Bagshaw et al. conducted a multicentre study in Canadian Intensive Care Units' (ICU) looking at frailty in 421 patients. Bagshaw utilised trained assessors to apply the CFS to all patients aged over 50 years of age at the time of ICU admission. They found that frailty was present in one in three patients and was associated with an increased risk of both hospital, adjusted odds ratio 1.81, (CI 1.09–3.01) and 12-month mortality, adjusted hazard ratio 1.82, (CI 1.28–2.60), when compared to non-frail patients (Bagshaw et al. 2014). A follow-up study indicated that frail patients had significantly lower quality of health scores at 6 and 12 months (Bagshaw et al. 2015). A major limitation of this study was that only one in three

Table 1. Major Studies Exploring Frailty in the Critically Ill

Author	Year	Study Type	Population	Patient Number	Frailty Assessor	Frailty Model	Outcomes of frail patients
Bagshaw	2014	Multi-centre prospective cohort study	ICU patients aged > 50 years	421	Trained research co-ordinator	CFS	Increased in-hospital and 12-month mortality; Increased functional dependence
Le Maguet	2014	Multi-centre prospective observational	ICU patients aged > 65 years	196	Patient or patient's relative	Fried Phenotype (FP) CFS	Increased ICU, in-hospital and 6-month mortality (CFS), ICU mortality (FP)
Fisher	2015	Single centre prospective observational	All ICU patients	229	Next of kin or Senior Nursing staff	CFS	Increased hospital length of stay (LOS), nil impact upon ICU mortality or LOS or hospital mortality
Bagshaw	2015	Multi-centre prospective cohort	ICU patients aged > 50 years	421	Trained research co-ordinator	CFS	Decreased QoL at 6 and 12 months, increased functional dependence and disability
Masud	2013	Retrospective Chart Review	Burns patients aged >65 years admitted to ICU	42	Principal Surgical Investigator	CFS	Less surgical intervention Higher 12-month mortality
Charles	2011	Retrospective Chart Review	ICU patients aged > 80 years	112	Principal Medical Investigator	CFS	Frailty Score not associated with survival or predictive of mortality

ICU = Intensive Care Unit, CFS = Clinical Frailty Scale, QoL = Quality of Life

of all eligible patients was included, questioning the practical application of frailty assessment in critically ill patients.

In France Le Maguet et al. performed a multicentre observational study of 196 patients aged greater than 65 years to investigate frailty, and employed both the Fried frailty phenotype and the CFS. This study permitted either the patient or their relatives to provide the necessary information to assign a frailty score. Frailty was found to be present in 41% and 23% of patients, using the Fried phenotype and the CFS, respectively. In this study, frailty, as defined by Fried's phenotype, was three times more likely to be associated with ICU mortality. In addition a CFS >4 was significantly associated with hospital and 6-month mortality (Le Maguet et al. 2014). However, the high number of patients with traumatic brain injury (20%) or admitted post cardiac arrest (8%) potentially confounded and reduced the generalisability of these findings.

Other research has focused on more specific sub-groups of critically ill patients with the CFS. Masud et al. assessed the correlation of frailty with outcome in elderly patients with severe burns. They found that frailty was associated with less surgery and higher mortality at 12 months (Masud et al. 2013).

Unfortunately, the correlation of frailty and adverse outcomes is not consistent in studies of the critically ill. In a retrospective assessment of over 100 patients aged greater than 80 years from the United Kingdom, Charles et al. (2011) found no correlation between the frailty score and adverse patient outcomes. Fisher et al. (2015) utilised the CFS in a single centre study of over 200 patients in an Australian tertiary hospital. They found that frailty, as defined by the CFS > 4 had a prevalence of 13%, was more common in chronic liver and chronic renal disease patients, and was significantly associated with increased hospital length of stay but not ICU or hospital mortality. In contrast to other studies Fisher et al. applied the CFS to all patients admitted to the ICU regardless of age and used a patient's next of kin, or senior nursing staff when next of kin were unavailable, to assign the CFS score. Consistent with other studies of frailty in the critically ill, only half of all eligible patients were able to be included in the study (Fisher et al. 2015).

Whilst current ICU predictive tools use age and co-morbidities in their models, they incorporate a very limited assessment of patients' pre-morbid function. Interestingly, within both Bagshaw's and Le Maguet's studies there appeared to be no significant difference in ICU illness severity scoring between frail and non-frail patients. This suggests that the assessment of frailty may potentially be an adjunct to existing predictive tools in quantifying a patient's pre-morbid reserve and post ICU discharge outcome.

Further confounding the role of frailty in the critically ill has been the suggestion that an episode of critical illness may rapidly accelerate a patient's pre-frail state or lead to the development of many of the characteristics of frailty. Baldwin et al. explored this in patients with respiratory failure who required ICU admission. Frailty was assessed immediately prior to hospital discharge via the Fried phenotype model. This study found frail patients had a 6-month mortality of 41%, and that with each increased Fried phenotype domain mortality increased three-fold (Baldwin et al. 2014). The application of frailty scoring at discharge may allow greater quantification of the physical, nutritional, cognitive and psychological disabilities of ICU survivors. This in turn may allow directed interventions to minimise long lasting sequelae.

Choice of Assessor

The ideal person needed to assess frailty in critical care is currently unknown. In the community, geriatricians have formal training and expertise in recognising and managing frail patients and accordingly are shown to have high inter-rater reliability (Rockwood et al. 2005; Rockwood et al. 2007). However, it is unclear whether this consistency exists outside this setting. In the studies performed in the critically ill, a variety of assessors have been used and there is no published data assessing their inter-rater reliability. Bagshaw et al. (2014;2015) utilised trained assessors to assign scores. Le Maguet (2014) and Fisher et al. (2015) utilised the patient's next of kin or, in their absence, a senior ICU nurse. Interestingly, in the latter study there was no statistical difference between the frailty scores assigned by these two methods. The problem of variability in inter-rater reliability was highlighted by Hii et al., who found that non-geriatrician clinicians were unable to accurately diagnose frailty and varied significantly in classifying frailty (Hii et al. 2015).

Conclusions

Frailty may be an important factor in predicting patient outcome in ICU and is being increasingly studied in different patient populations. Prevalence is approximately 1 in 5 of elderly patients in the community and is even higher in those undergoing major surgery or experiencing critical illness. Although evidence for a strong association between frailty and outcome exists in the community, current evidence suggests an inconsistent association between frailty and adverse patient outcomes in the critically ill. In addition, it remains unclear which tool is most appropriate to use for the assessment of frailty in ICU and who should be making such assessments. Further research is required into the assessment of frailty in the critically ill before its routine use can be recommended for prediction of outcome after ICU admission. ■

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ANTIMICROBIAL COPPER TOUCH SURFACES

REDUCE INFECTIONS, LIBERATE RESOURCES AND CUT COSTS

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The role of the environment in the transmission of healthcare-associated infections (HCAIs) is increasingly recognised, requiring a new approach to the selection of materials for objects frequently touched by healthcare workers, patients and visitors that can serve as reservoirs of infection.

There are many technologies and materials on the market, but none are as effective under typical indoor conditions as copper, and its hygienic properties are far from new to us. The Ancient Egyptians, Greeks and Romans used copper-based preparations to treat ailments and prevent wound infections, and in India drinking water is traditionally stored in pots made of brass — an alloy of copper and zinc.

Evidence shows that upgrading the most frequently-touched surfaces in a healthcare environment to antimicrobial copper can reduce the spread of costly infections and improve patient care. This article explores the growing body of research — from laboratory tests and clinical trials — and considers the practicalities and economics of upgrading key surfaces to copper.

Effective Under Typical Indoor Conditions

Copper's antimicrobial properties have been documented in scientific literature for more than a century, but it was not until 2000 that its efficacy against the pathogens responsible for HCAIs began to be assessed.

Fifteen years on, more than 60 papers report copper's broad-spectrum, rapid efficacy against bacteria, viruses and fungi — including MRSA, E. coli, Influenza and norovirus. No pathogen tested has been able to survive on copper.

Claims of antimicrobial efficacy made for many antimicrobial products are based on Japanese Industrial Standard (JIS) Z 2801, *Antibacterial products - Test for antibacterial activity and efficacy* (Japanese Standards Association 2012) and International Organization for Standardization (ISO) 22196: 2011 - *Measurement of antibacterial activity on plastics and other non-porous surfaces* (ISO 2011) tests, conducted at >90 percent humidity, 35°C and over 24 hours under a plastic film. These basic tests are described as a proof of principle and do not indicate how a material will perform in the field.

To better represent actual in-use conditions when testing copper, researchers developed new protocols to reflect typical room temperature and humidity and used representative contaminants.

The U.S. Environmental Protection Agency (EPA) approved one such test method and developed further protocols — including a challenging recontamination test — leading to the registration of hundreds of copper alloys to be marketed in the U.S. with public health claims. These were the first solid materials to achieve such recognition. As a general rule, alloys should have a minimum 60 percent copper content, and the higher the copper content, the faster the kill (in laboratory tests).

Figure 1 shows the results of an EPA recontamination test simulating a splash or sneeze — a 'wet' contamination event — with MRSA applied every three hours over a 24-hour period at room temperature and humidity. The number of MRSA used (1 million colony forming units per square inch) is far higher than would be found in a typical contamination event. On copper, the MRSA are totally eliminated before the next recontamination, while there is survival and significant growth on the stainless steel control (Michels et al. 2008).

Laboratory research on the antimicrobial efficacy of copper and copper alloys has been carried out and verified at institutions around the world, with results peer-reviewed and published in respected journals. They exhibit efficacy under typical indoor conditions, unlike silver-containing materials and triclosan, which showed no antimicrobial efficacy under these conditions, as shown in **Figure 2** (Michels et al. 2009).

Simulations of 'dry' touch contamination events have also been developed, and these tests show an even more rapid kill, with 106 vancomycin-resistant enterococci (VRE) killed in less than 10 minutes on 1cm^2 copper (Warnes et al. 2011).

A leading researcher in this field is Professor Bill Keevil, Chair in Environmental Healthcare at the University of Southampton, and his work includes investigation of the mechanisms by which copper exerts its antimicrobial effect.

For bacteria, the current consensus among researchers is that there are several probably interacting mechanisms, including:

- Causing leakage of potassium or glutamate through the outer membrane of bacteria;
- Disturbing osmotic balance;
- Binding to proteins that do not require copper;
- Causing oxidative stress by generating hydrogen peroxide;
- Degradation of bacterial DNA.

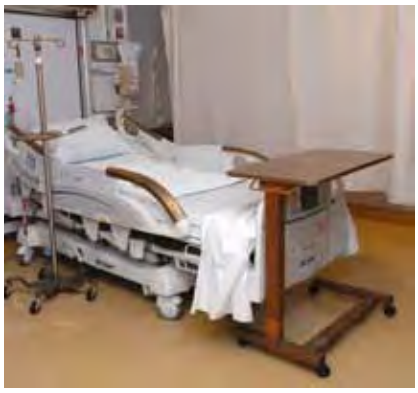
There is also agreement that bacteria will not develop resistance to copper. Professor Keevil explains: "Copper works in completely different ways to antibiotics or common biocides. It punches a hole in the cell membrane, like a balloon, and the bacteria collapse. It stops them respiring, goes into the cell and destroys their DNA.

Mutation happens because you get small changes in DNA in cells. The beauty of copper is it destroys the DNA; there is nothing left. We've shown this for bacteria, fungi and viruses. They can't mutate. They have no time."

Most recently, the Southampton team has investigated the contribution antimicrobial copper surfaces can make to combating the rise of antibiotic resistance, assessing the ability of two different strains of bacteria to pass genetic

The Bostonian Sleep Clinic - UK
Image credit: Brass Age

Isku Medical Centre - Finland
Image credit: Copper Development Association



Ralph H. Johnson VA Medical Center - US - Clinical Trial Site

material conveying antibiotic resistance between them on copper and stainless steel. While this took place on stainless steel, it did not happen on copper (Warnes et al. 2012).

Copper can therefore contribute to the fight against antibiotic resistance in two ways: by reducing the spread of infections and thus the need for antibiotics and by preventing the transfer of resistance between bacteria on surfaces.

Furthermore, research published at the end of 2015 by the University of Southampton has found copper can effectively help to prevent the spread of respiratory viruses (Warnes et al. 2015).

Animal coronaviruses that 'host jump' to humans, such as SARS and MERS, result in severe infections with high mortality. The new research found that a closely-related human coronavirus – 229E – can remain infectious on common surface materials for several days, but is rapidly destroyed on copper.

Lead researcher Dr Sarah Warnes said: "Transmission of infectious diseases via contaminated surfaces is far more important than was originally thought, and this includes viruses that cause respiratory infections. This is especially important when the infectious dose is low and just a few virus particles can initiate an infection.

"Human coronavirus, which also has ancestral links with bat-like viruses responsible for SARS and MERS, was found to be permanently and rapidly deactivated upon contact with copper. What's more, the viral genome and structure of the viral particles were destroyed, so nothing remained that could pass on an infection. With the lack of antiviral treatments, copper offers a measure that can help reduce the risk of these infections spreading."

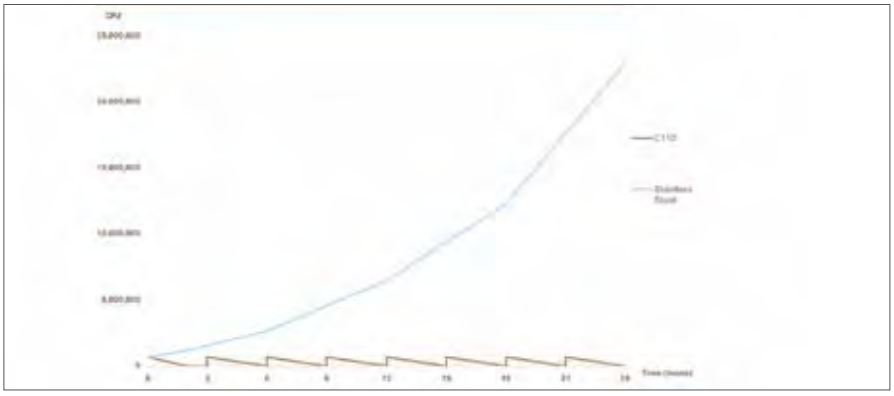


Figure 1. EPA Recontamination Test to Simulate a Busy Ward: 1 million CFUs of MRSA every 3 Hours on Copper (C110) and Stainless Steel
Source: Grass et al. (2010)

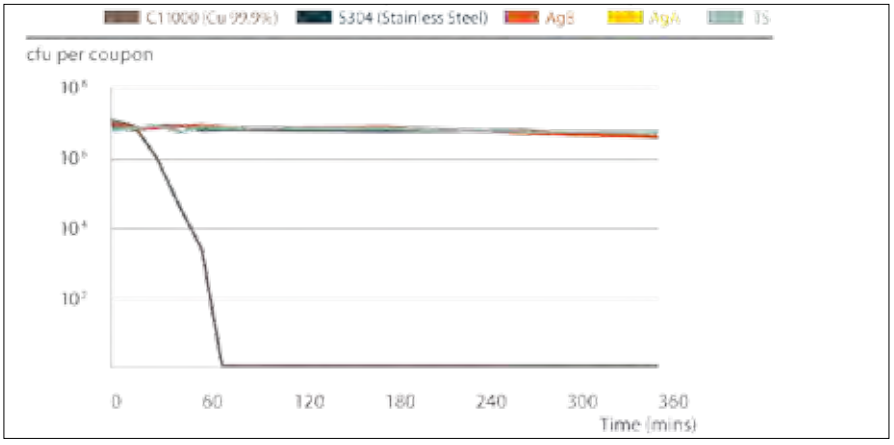


Figure 2. MRSA Viability on copper, silver- and triclosan-coated materials and stainless steel at room temperature and humidity
Source: Michels et al. (2009)

Proven Under Challenging Clinical Conditions

Having established the inherent ability of copper to eliminate bacteria and viruses in the laboratory, the next logical step was to discover how this would translate into real clinical environments. It is important to note that trials have used solid materials, as the effective surface will not wear away or be susceptible to reduced efficacy over time, as with coatings and composites.

How Copper can Help Protect Your Patients

By choosing touch surfaces made from antimicrobial copper, you can continuously kill pathogenic microbes, boosting hand hygiene, cleaning and disinfection measures and creating a safer environment for your patients. This novel approach works 24/7 and requires no routine maintenance, just standard cleaning. Antimicrobial copper surfaces are made from solid, eco-friendly metals with intrinsic antimicrobial properties that last the lifetime of the product.

Antimicrobial copper touch surfaces offer:

- Continuous and significant bioburden reduction
- Improved patient outcomes
- A supplement to standard hygiene practices
- Simple, cost-effective intervention
- Payback in less than one year

Online Product Directory

Hospital Manager's Guide to Antimicrobial Copper

www.antimicrobialcopper.org

Antimicrobial Copper Cu+

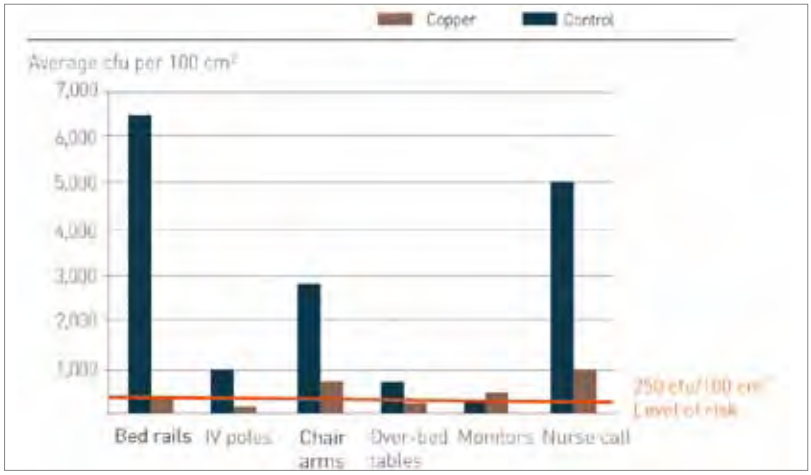


Figure 3. Sustained Reduction of Microbial Burden on Hospital Surfaces Through Introduction of Copper
Source: Schmidt et al. (2012)

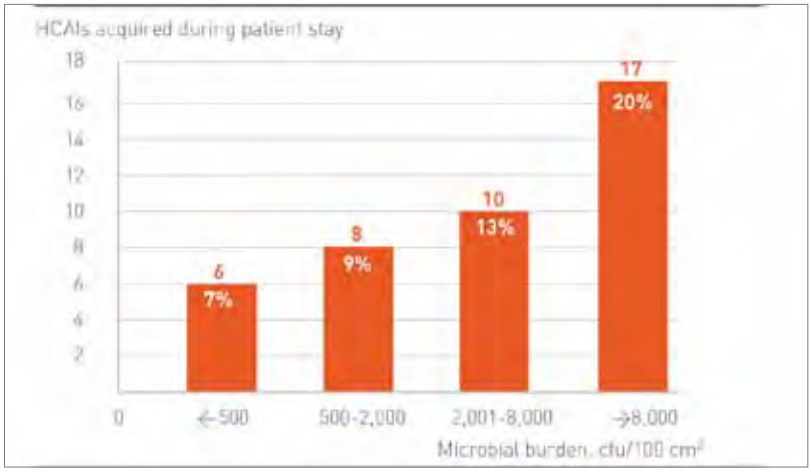


Figure 4. Quartile Distribution of HCAIs Stratified by Microbial Burden
Source: Salgado et al. (2013)

Pathogens persist on standard clinical touch surfaces, creating reservoirs of infection that pose a risk to patients, staff and visitors, for days, weeks or even months. The first clinical trial – undertaken at Selly Oak Hospital in Birmingham, UK – found that antimicrobial copper taps, toilet seats and door handles on a general medical ward had 90 to 100 percent fewer bacteria on them than the same items made from standard materials (Casey et al. 2009).

Numerous trials have since been conducted in different healthcare systems — including the U.S., Germany and Finland — and different clinical environments such as nephrology, geriatric and ICU wards. They have similarly reported significant and continuous bioburden reduction, with trial leaders concluding that antimicrobial copper surfaces can provide an additional measure to reduce the spread of HCAIs.

A multicentre clinical trial in ICUs, funded by the U.S. Department of Defense, took the research one step further and asked the question "Will the bioburden reduction associated with the installation of copper surfaces reduce the number of infections?" Led by Dr. Michael Schmidt, Professor and Vice Chair of Microbiology and Immunology at the Medical University of South Carolina, the trial team found that replacing just six key, near-patient touch surfaces reduced the incidence of infections by 58 percent (Salgado et al. 2013). **Figure 3** shows the accompanying reduction in microbial burden on the six surfaces (Schmidt et al. 2012).

Just 10 percent of touch surfaces were upgraded to antimicrobial copper, yet the impact was significant. This study is the first to report a correlation between environmental bioburden (whether in copper or control rooms) and the risk of acquiring an infection, and to show a reduction in that risk due to a minimal intervention with an effective antimicrobial material.

Figure 4 demonstrates this correlation, with quartile distribution of HCAIs stratified by microbial burden measured in the ICU room during the patient's stay. There was a significant burden association between burden and HCAI risk, with 89 percent of HCAIs occurring among patients in rooms with a burden of more than 500 colony-forming units (CFU) per 100 cm^2 (Salgado et al. 2013).

Key healthcare watchdogs and horizon scanning bodies around the world, including ECRI Institute (2014) and the Canadian Network for Environmental Scanning in Health (Ndegwa 2015) have recognised the growing body of evidence for copper's potential to boost infection control. It has also been acknowledged in the evidence-based epic3 guidelines, which

Table 1

Medical Equipment & Furniture	Fixtures & Fittings	
Bed rails*	Cabinet handles*	Light switches*
Chairs*	Counter tops	Push plates*
Dressings trolleys	Dispensers	Sinks*
Input devices/nurse call buttons*	Door handles*	Switched sockets
IV poles*	Grab rails*	Taps
Over-bed or tray tables*	Hand rails	Toilet seats and flush handles*

Source: Copper Development Association (2014)

included copper as an emerging technology in 2014 (Loveday et al. 2014).

With this proven efficacy in mind, the next question arising will naturally concern the cost of installing antimicrobial copper touch surfaces.

Cost Benefits of Upgrading to Copper

HCAIs are very common and very costly, both financially and in terms of human life. Approximately 20 percent of ICU patients in European hospitals get HCAIS, and in 2011 they affected 4.1 million patients, necessitating 16 million extra days in hospital. Thirty-seven thousand deaths were recorded as being caused by HCAIs, plus 110,000 deaths where they were a contributing factor, and they had a direct clinical cost in excess of 7 billion euros (World Health Organization 2011).

York Health Economics Consortium (YHEC), a group of leading global health economists based at the University of York in the UK, developed a fully-referenced cost benefit model for hospital managers to illustrate the economic rationale of an antimicrobial copper installation (Taylor et al. 2013). The model is based on the cost of installing antimicrobial copper touch surfaces and the balancing cost savings resulting from reduced infection rates. The model allows local data to be entered for site-specific evaluations, but is populated with default data for the UK as an illustration.

Using UK data for cost of infection, industry data for cost of antimicrobial copper and standard components, and a conservative infection rate reduction of 20 percent (where the U.S. trial reported a 58 percent reduction), the model considers a planned refurbishment or new build. It predicts that the cost of replacing the six key touch surfaces in a 20-bed ICU with antimicrobial copper equivalents will be recouped in less than two months, based on fewer infections and the resulting shorter lengths of stay. It also calculates a positive impact on bed days and quality-adjusted life years offered by antimicrobial copper.

Dr. Matthew Taylor, YHEC's director and one of the model's authors, concludes: "After the initial two months, ongoing cost savings will accrue from the reduction in blocked beds and better directed staff resources."

Specifying Copper

There is an ever-expanding range of products on the market as the supply chain responds to growing demand, so how does one get started with selecting the priority touch surfaces to upgrade in a given healthcare environment?

A number of studies have identified frequently-touched surfaces as being contamination hotspots that present an infection risk and are therefore targets for upgrade. Based on a review of international research, the United States Centers for Disease Control and Prevention (CDC) published a checklist of key surfaces based upon the likelihood of touch and contamination (Guh et al. 2015).

In the many copper clinical trials conducted around the world multidisciplinary teams have prioritised high frequency touch surfaces to upgrade to copper. The factors considered include known hotspots from microbiological testing and likely hotspots based on experience and understanding of staff/patient/visitor dynamics.

Table 1 represents a summary of these surfaces with CDC surfaces indicated by an asterisk, to differentiate from those identified in clinical trials, and is the starting point for selecting items to upgrade for any new build or refurbishment project.

Input should also be sought from the infection control team and ward staff to ensure that all high-risk touch surfaces specific to a particular area are included. The regular environmental swabbing carried out by infection control teams to assess the state of cleanliness will also indicate contamination.

Support with identifying efficacious products is available in the form of an industry stewardship scheme. The Antimicrobial Copper brand and Cu^+ mark are used by leading manufacturers of hospital equipment, furniture and fittings to indicate their products are made from solid antimicrobial copper, and that the organisation adheres to strict usage rules guiding their understanding of the underlying technology and its deployment.

An online directory of approved products is available to browse on antimicrobialcopper.org.

Copper alloys offer a wide palette of colours from the gold of brasses to the rich brown of bronzes right through to the silver/white shades of copper-nickels. Copper alloys will naturally darken over time, but this does not impact their antimicrobial efficacy. More colour-stable alloys traditionally used in naval applications are available.

Wide Installation

Antimicrobial copper surfaces are an adjunct to and not a replacement for existing infection control measures. Alongside good hand hygiene and regular surface cleaning and disinfection, they will continuously reduce surface contamination and consequently the risk of infections being passed between people via these surfaces.

Installations have already taken place around the world in more than 25 countries. In these hospitals, the importance of taking a multidisciplinary approach to infection control has been clear.

Further Reading

You can download a simple, four-page guide Antimicrobial Copper: A Hospital Manager's Guide (CDA Publication 219) (2014) from News and Downloads/Brochures on antimicrobialcopper.org. ■

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SIX STEPS TO IMPLEMENT BEDSIDE ULTRASONOGRAPHY IN CRITICAL CARE

A ROADMAP TO RAPID IMPROVEMENTS IN PATIENT SAFETY

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This article will provide an overview of how to accelerate adoption of bedside ultrasonography, based on experience in a large hospital system. Developing an evidence-based ultrasound training programme and the economic benefits of proven safety practices, such as ultrasound-guided central venous catheterisation (CVC), will be addressed.

Every day, more than 1,000 patients die in the United States from preventable hospital errors (Hospital Safety Score 2015). Ultrasound at the bedside is an extremely valuable tool for improving the safety and quality of care for critically ill patients, while also helping reduce—or even eliminate—certain errors and associated costs. Applications in critical care range from ultrasound guidance of needle-based procedures to rapid assessment of the heart ("pump") and volume ("tank") in patients with congestive heart failure (CHF) or shock.

Steps to Fast-Track System-Wide Adoption of Bedside Ultrasound

Many medical centres, including Banner Health where I practise, now mandate ultrasound guidance for all CVCs. Headquartered in Phoenix, Arizona, Banner Health operates 28 hospitals and acute-care facilities, along with many ambulatory health centres and clinics, across seven states. In 2013, 256,000 patients were admitted to our hospitals, 675,438 patients were treated in our emergency departments, and our clinics managed 2,636,000 visits. With more than 45,000 employees, including about 7,000 medical staff members, Banner ranks among the United States' largest healthcare systems.

Banner Health has launched a system-wide initiative called Care Transformation that unites best practices in clinical care with leading-edge technology to provide better, safer care to our patients. This initiative is designed to reduce the time between identification of evidence-based clinical practices and their widespread adoption and implementation as a predictable part of daily care, including system-wide ultrasound-guided central-line placement and a bedside echocardiography programme with the ability to capture and interpret real-time ultrasound imaging on a 24/7 basis to monitor and guide treatment of ICU patients. Here is how this process worked at our system and lessons learned.

Step 1: Define clinical challenges to be solved by implementing bedside ultrasound

In the early 2000s, one of our chief nursing officers needed to place a PICC line (peripherally inserted central catheter) in a patient with difficult vascular access. She borrowed a bedside ultrasound machine from the radiology department and successfully inserted the line. This success motivated other clinicians to adopt this approach, initially with informal person-to-person training, followed by small pilot programmes supported by local department budgets.

Establishing vascular access is one of the most commonly performed hospital procedures, with several million central lines placed annually in U.S. hospitals. Up to 78% of critical patients have a CVC inserted at some point during their hospital stay (Gibbs and Murphy 2006), with a documented mechanical complication rate of up to 19% (McGee and Gould 2003), when landmark-based techniques are used.

Step 2. Examine the scientific evidence and safety benefits of bedside ultrasound

Procedural complications are among the most common—and costly—medical errors, according to a recent analysis (Van Den Bos et al. 2011). Of the errors analysed, iatrogenic pneumothorax (the accidental puncture and collapse of the patient's lung during medical treatment, such as CVC), was one of the most expensive, costing the U.S. healthcare system $580 million in 2008. This complication can lengthen hospital stay by 4 to 7 days, at an additional cost of up to $45,000 (Zhan et al. 2004).

If eliminating such serious safety risks as pneumothorax sounds impossibly ambitious, consider these findings: in a randomised trial that included 401 critical care patients (Fragou et al. 2011), ultrasound-guided CVC reduced rates of pneumothorax and haemothorax to zero, versus rates of 4.9% and 4.4% respectively when landmark methods were used. All other complications were also reduced or eliminated with ultrasound.

Based on robust safety data from multiple studies, evidence-based guidelines from numerous medical societies and government agencies, including the U.S. Agency for Health Research &

Quality (AHRQ) (Shojania et al. 2001), the U.S. Centers for Disease Control and Prevention (CDC) (2011), and the UK National Institute for Health and Care Excellence (NICE) (2002), recommend ultrasound guided placement of central lines as a preferred safety practice.

Step 3. Identify an ultrasound champion and launch a bedside ultrasound training programme

A lesson learned from our experiences is the importance of physician leadership to accelerate adoption of bedside ultrasound. One of our physicians, Dr. Gregory Chu, not only was an early champion of this technology, but also played an important role in developing a training programme to teach respiratory therapists how to insert CVC under ultrasound guidance.

Respiratory therapists were selected as ultrasound trainees for two reasons. First, they are available 24/7 at our hospitals and therefore could perform middle-of-the-night CVCs as needed. Previously, only physicians could place central lines, creating workflow issues and strain on the emergency department when this procedure was needed at unusual hours. Second, our respiratory therapists had already been trained in ultrasound-guided PICC line insertions, so were experienced with this imaging technology.

Our training programme leveraged both internal and external resources. Our simulation centre was employed to provide training with virtual patients, followed by hands-on training with actual patients. We also partnered with our ultrasound provider, which offered such resources as access to CVC protocols used at other institutions and help with organising training events.

To accelerate diffusion of ultrasound-trained clinicians, Dr. Chu and other physicians trained the initial cohort of respiratory therapists, who then became ultrasound trainers themselves after demonstrating proficiency in central-line placement. All Banner's residents also received the training, facilitating swift adoption of ultrasound guidance across our hospital system.

Step 4. Use clinical teams—and CVC safety bundles that include ultrasound guidance

Banner established dedicated vascular-access teams comprising respiratory therapists and nurses, available around the clock to perform ultrasound-guided line insertions. To reduce central-line associated bloodstream infections (CLASBIs), our health system uses a six-point safety bundle:

1. Hand hygiene;
2. Maximal barrier precautions;
3. Chlorhexidine skin antisepsis;
4. Optimal catheter site selection;
5. Daily review of CVC line necessity, with prompt removal of unneeded lines;
6. Ultrasound-guided line placement.

About 30% of ICU patients suffer one or more healthcare-associated infections (HAIs), according to the World Health Organization (WHO) (2016). About 75,000 hospitalised patients die from HAIs annually, with CLASBIs causing death rates ranging from 12 to 25 percent.

Hospitals that use central-line safety bundles that include ultrasound guidance have seen striking reductions in CLASBIs—or in some cases, have even eliminated them. For example, White Memorial Hospital in Los Angeles, California achieved a rate of zero between January 2010 and August 2011 at the 353-bed hospital, while also avoiding pneumothorax complications.

Step 5. Expand use of bedside ultrasound to new applications, such as bedside echocardiography

Our bedside echocardiography programme was also inspired by a clinical challenge, which occurred at 3 AM when a consulting ICU physician, Hargobind Khurana, was called to diagnose a patient in shock. He ordered an echocardiogram, but discovered that no cardiologist would be available to interpret the echo until later that morning. Since the results were needed immediately, to guide treatment of the critically ill patient, he asked a tele-intensivist in our iCare remote access centre to review the scan in real time.

In minutes, with the help of the tele-intensivist, Dr. Khurana was able to accurately evaluate cardiac output and intravascular volume, diagnose the patient and initiate lifesaving treatment. This case demonstrated the need to capture and interpret cardiovascular ultrasound images at any hour of the day or night to guide treatment in real time. Banner decided to partner with the iCare team's 24/7 capabilities, through remote consultation, as a recommended clinical practice for adult critical care.

As part of the bedside echo programme, respiratory therapists were trained to acquire high-quality bedside ultrasound images to transmit to the tele-intensivists remotely. All iCare intensivists were trained in interpreting echo images in real time and using the findings to assess the fluid and cardiovascular status of patients suffering from CHF, shock or other conditions.

In May 2015 the Surviving Sepsis campaign issued an updated, evidence-based bundle of care practices for patients with severe sepsis or septic shock (Surviving Sepsis Campaign 2015). Bedside cardiovascular ultrasound was one of the recommended methods for evaluating volume status and tissue perfusion, with the scan to be performed with six hours of clinical presentation.

> **"broad engagement of physicians through educating them about safety benefits of ultrasound guidance"**

The rationale for implementing bedside echo also drew on studies citing the following benefits:

- Improved diagnostic accuracy;
- Reduced time delays for procedures;
- Superior accuracy in evaluating fluid status in heart failure patients, compared to physical examination techniques;
- Reduced cost for procedures;
- Support for use of ultrasound as the 'third eye' to help the intensivist manage patients;
- Assessment of shock to determine haemodynamic status, fluid resuscitation and interventions.

Step 6: Track ultrasound outcomes—and learn from success

Over the past three years, our health system has avoided any complications associated with central line placement. A key component of this success has been broad engagement of physicians through educating them about safety benefits of ultrasound guidance, including confidence that the needle is inserted correctly

with a high degree of first-pass success. In this case, seeing truly is believing—in the power of ultrasound to truly transform the standard of care, particularly for those who need it the most: the critically ill.

Similarly, our bedside echo programme represents an exciting innovation in visual medicine: enhanced ability of intensivists—both at the bedside and via remote access tele-ICUs—to literally see how well the patient's heart is working and response to treatment in real time, allowing rapid adjustments in therapy if needed. As R. Adams Cowley, MD, the pioneering founder of the first U.S. shock trauma centre, famously observed, for critically ill or injured patients, "there is a golden hour between life and death" (University of Maryland Medical Center n.d.). With ultrasound at the bedside, and the clinical information it provides, physicians are ideally equipped to rapidly help the sickest patients achieve optimal outcomes. ■

Abbreviations

CHF congestive heart failure
CLASBI central line-associated bloodstream infections
CVC central venous catheterisation
HAI hospital-associated infections
PICC peripherally inserted central catheter

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Brainstorming: "Big Questions for the Experts"

Hotel Boscolo Exedra, Nice, France, May 1-4, 2016

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TRANSFORMING MEASUREMENT INTO UNDERSTANDING

QUANTITATIVE BEDSIDE DECISION SUPPORT

Intensivists today are faced with a growing deluge of quantitative data, along with demands to implement evidence-based protocols of increasing number and complexity. The tools to support such implementation, including computerised decision support, have, however, seen only incremental development over the past decades. This article will attempt to provide an analysis of the underlying causes and suggest possible structural and technological remedies.

Quantitative Data Sources

Since its inception, intensive care medicine has been one of the fields of medicine with the highest density of quantitative data derived from direct physiological measurement, as well as methods used across most clinical domains, such as laboratory and imaging results. Measurement technology has evolved continuously, with recent developments in molecular biology and medical technology promising a plethora of additional quantitative data sources from novel biomarkers, high throughput -omics technologies, quantitative imaging and innovative physiological sensors. Integration of these data sources into a patient-specific decision support framework may help to realise the potential of the "precision medicine" of tomorrow (Celi et al. 2014; Mertz 2014).

Data Deluge: Challenges in Translating Measurement to Understanding to Outcome Improvement

The traditional approach to transforming quantitative data into beneficial clinical decisions has been based on assimilation and integration of all data by the responsible physician in a largely qualitative fashion. For example, quantitative lab results are typically evaluated based on their relationship to statistical result distributions in the healthy population ("normal values"), and possibly their qualitative trends. A similar approach is taken to guiding therapy based on continuous physiological measurements such as arterial blood pressure. For long-established haemodynamic parameters, such as central venous pressure, this approach has been demonstrated to be largely ineffective for guiding fluid management (Marik et al. 2008). Furthermore, studies of the effects of established haemodynamic measurement techniques of unquestionable pathophysiological relevance such as the Swan-Ganz catheter have failed to demonstrate positive effects on outcome (Harvey et al. 2005; Rajaram et al. 2013). Appropriate patient selection and data interpretation have been identified as a key issue in these contexts (Vincent et al. 2008). The systematic translation of quantitative measurements into effective clinical decisions is an important current challenge in intensive care medicine, which will only become more daunting as our ability to measure continues to expand.

Medical science has provided numerous approaches to post-processing the available measurements to obtain more directly interpretable and relevant data to support effective clinical decisions. In the haemodynamic monitoring field, these include simple but effective dynamic markers of fluid responsiveness and the well-developed field of pulse contour analysis of arterial blood pressure, some of which have recently been recommended for usage in the management of circulatory shock (Cecconi et al. 2014). Another example is the wide field of physiological variability quantification, the potential of which in the critical care setting has long been recognised (see, e.g. Buchman et al. 2002). Technically more challenging is the utilisation of mechanistic mathematical models of (patho-)physiology for clinical data interpretation, prediction, and control (Zenker 2009; Zenker et al. 2007), in particular when addressing the safety-critical issue of uncertainty quantification. This holds the promise of not only meaningfully incorporating pathophysiological knowledge from centuries of physiological science, but also enabling the application of powerful techniques from the engineering domain to quantitative decision support in medical settings.

Translating Scientific Progress to the Bedside: Technological Developments, Market Structure and Regulatory Environment

Status Quo

Even though numerous approaches to making more of available measurements have been developed and prospectively validated, the level of available evidence to support their use and routine availability at the bedside is still limited. This may partially be attributed to the fact that although many innovative derived parameters can be computed from routine measurements, they are typically made accessible in the form of a separately sold "box", (or a new model of a general-purpose patient monitoring system), which encapsulates a vendor-specific implementation of the post-processing algorithm. This situation has several consequences:

- The innovation cycle of available post-processing algorithms is largely determined by the hardware life cycle, rather than the software and knowledge innovation cycle.
- The cost of bringing innovative techniques to the beside is exacerbated, since software innovation is, often unnecessarily, tied to

hardware replacement and unnecessary hardware redundancy often requiring additional disposable materials, contributing to the already significant resource utilisation in intensive care medicine.
- A large variety of vendor-specific implementations of very similar ideas with undefined differences in practical behaviour and applicability are marketed, leading to an inefficient dispersion of resources available for vendor-independent validation of their utility satisfying the criteria of evidence-based medicine.

There appear to be at least two major factors contributing to this situation:

a) Routine use of any technology at the bedside requires commercially available solutions. Development of such solutions is driven by their revenue potential, which, in the medical device market, has traditionally been concentrated in hardware and particularly in the disposable segment.
b) The regulatory environment has traditionally focused on the single manufacturer providing a medical device as a closed system (either a single "box" or an integrated system of devices including the connectivity infrastructure, as was typically the case for monitoring systems with distributed alarm functionality). The manufacturer guarantees a specified functionality for the intended use of the medical device and takes responsibility for managing risks associated with the system according to the state of the art as defined by norms such as ISO 14971: 2007, *Medical devices -- Application of Risk Management to Medical Devices* (ISO 2007), among others.

With regard to a), the increasing market penetration of electronic documentation systems in intensive care has forced increasing integration of the medical device infrastructure with the hospital information technology (IT) infrastructure. Such documentation systems, in particular with a view to integrating decision support functionality, may themselves be classified as medical devices/products (typically of risk class IIa in the German market) (Mania 2012). They are thus subject to associated regulatory requirements with regard to implementing state-of-the-art operational procedures (European Commission 2012; Council Directive 1993). However, the challenges of achieving reliability levels typical of medical device setups for more generic data streams relevant to therapeutic decision making involving various IT subsystems (such as lab results) remain largely unaddressed. Key components of the data processing chain are typically not classified as medical devices and, consequently are not subjected to the same level of quality assurance and risk control procedures. To add to the overall complexity of the current situation, economic as well as technological constraints have led to a wider implementation of traditional medical device solutions (distributed alarm systems again providing a prominent example) that piggyback on regular IT infrastructure by, e.g., using the hospital IT network for inter-device connectivity and alarm propagation. This is the other side of the coin of IT/medical technology convergence. Such setups require a different approach to managing the risks associated with their operation, since no single manufacturer can be held responsible for the functionality of the system as a whole. The relatively recent norm IEC 80001 (ISO 2010-2015), *Application of risk management for IT-networks incorporating medical devices* (ISO 2010), provides guidance for risk management of IT networks incorporating medical devices and addresses key properties such as safety, effectiveness and data and system security. As opposed to the traditional "box" situation, the "responsible organisation" (typically the hospital) now bears responsibility for managing the risk of the entire setup in a structured fashion. Each manufacturer of medical device components of the system is obliged to provide customers with sufficient device-specific information to enable structured risk management. These often unrecognised and unaddressed responsibilities entail both challenges and opportunities.

A key challenge in implementing such state-of-the-art risk management is the additional effort and highly qualified personnel required, which entails additional cost at a time when economic constraints already affect healthcare delivery.

Turning Challenge into Opportunity

Since hospital-side structured risk management of complex interconnected IT and medical device systems from various vendors may now be required anyway, a fundamental hurdle to restructuring the entire information processing pipeline incorporating both medical device data sources and other clinically relevant quantitative data such as laboratory results and imaging data towards a more robust, flexible and dynamic model that would enable more effective and efficient translation of scientific insight into computer-supported bedside decision support integrating all these data, can now be addressed proactively.

An obvious approach for such restructuring, using intensive care patient monitoring as an example, would be modelled on the concept of modularity and open interface standardisation. This concept is hugely successful in almost all areas of engineering and technology. In this case it would be designed specifically to enable a structured risk management approach to the system as a whole. Naturally the conceptual framework extends to the entire quantitative data flow surrounding patient care. Risk management becomes more central as physicians have to, for practical purposes, often exclusively rely on information that has been processed in a chain of interconnected devices and IT subsystems currently not subject to structured risk management as established in the traditional medical device sector.

> **"highest density of quantitative data derived from direct physiological measurement"**

For example, if, in the haemodynamic monitoring domain, physiological measurement and signal conditioning, digital postprocessing and visualisation were decoupled and connected via standardised interfaces (Zenker et al. 2012), several advantages could be reaped:

- The threshold to market entry for postprocessing technology would be lowered since "software only" solutions would become marketable, increasing the breadth of potential contributors of innovative postprocessing solutions.
- The incentive to produce vendor-specific modifications of existing approaches with unproven or incremental benefit would be reduced:
- The whole breadth of downstream processing would become available as validated stan-

dard modules from specialised manufacturers (which of course could be identical with the hardware manufacturers);
- Competition of hardware vendors could focus on core competencies such as providing optimal signal quality, device reliability, and usability at competitive prices.
- Available public resources for vendor-independent evidence-based clinical validation of post-processing and visualisation technology could concentrate on reference implementations with significant innovation potential, thus increasing the evidence base for available and relevant tools.
- The innovation cycle for postprocessing and visualisation technologies could approach the fast cycles typical of the software industry.
- Broad availability of state-of-the-art post-processing and visualisation technology at the bedside could become affordable. Innovative functionality would become available at the cost of rolling out highly standardised software modules along with established structured risk management procedures rather than buying and installing new hardware.

Recent efforts of established vendors of data analytics solutions have yielded systems with some of the desired functionality, which have been deployed in academic settings (see e.g., Sow 2015). However, the implementation of modular systems that allow adequate structured risk management with the required level of automation of quality assurance procedures (automated unit tests at interfaces etc.) to keep risk control efforts under control in clinical settings critical to patient safety would require a concerted effort of medical device manufacturers, analytics providers, users and regulators. This should include interface standardisation that is sufficiently specific, with interoperability across these standardised interfaces included in the intended use of the medical device/software. In the current globally heterogeneous regulatory environment, a promising practical near-term solution to make progress in this direction may be for large manufacturers of medical devices or software to open up their closed systems to certified "app"-like analysis and visualisation components produced by third parties, similar to the way the mobile device industry has catalysed a massive innovation boost by creating a standardised application software "ecosystem" in which third parties can offer novel functionality with a relatively low market entrance threshold. Obviously, certification requirements for such medical "apps" would have to be more demanding than in the mobile device market, likely including formal validation steps and provision of manufacturer support for structured user-side risk management of the resulting setup. However, the obstacles appear technically surmountable and the potential yield with regard to enabling rapid and affordable translation of scientific insight to improved patient care appears high. Standardisation of the interfaces for such an "app" ecosystem across manufacturers would naturally be desirable, although if such a market were to gain momentum, de facto standards based on individual vendor specifications might emerge, as could repeatedly be observed in the digital audio signal processing industry over the past decades.

With regard to data streams currently viewed as lying outside of the medical device domain and the associated regulatory constraints, establishment of an infrastructural basis that would enable reliability and structured risk management comparable with the medical device sector, adequate for the emerging usage scenarios of potentially safety-critical bedside decision support beyond what the unaided human can implement, would serve to make explicit and supportable the already inevitable technological convergence of the medical device and software sectors. It would establish a solid and safe basis for implementing advanced clinical decision support technology without compromising patient safety. To keep risk management efforts manageable, a modular architecture that incorporates meaningful structured risk management by design and complies with regulatory constraints (which may also require adaptation in the long run) appears of critical importance.

Conclusions

A modular architecture for medical data acquisition, processing, and visualisation, based on open interface standards with associated structured risk management procedures incorporating at least partially automated quality assurance procedures evolved from existing standards in the medical device industry would enable implementation of state-of-the-art clinical decision support based on all available data that pushes beyond what the unaided human can achieve without compromising patient safety. In the absence of sufficiently detailed and provably workable interface specifications that would enable regulatory enforcement, incentives for implementation by manufacturers, aside from the intrinsic motivation of improving patient care, may come from the hugely successful examples provided by the mobile device industry, along with the commercial potential of a new market for providing risk management packages as a service to healthcare providers.

Failing that, it will be left to customers to demand meaningful structural innovation that enables state-of-the-art patient care at affordable cost and manageable risk.

Conflict of Interest

SZ is PI of the "AcuWave" project supported by the Dräger foundation, which aims at improving bedside availability of advanced postprocessing algorithms at the ICU bedside. ■

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DON'T FORGET TO ASK!

THE PATIENT AND RELATIVE PERSPECTIVE

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There has been good progress in the last decade to ensure that the patient voice is heard at all levels, including in research and service planning. However there is still more to be done, and this article sets out the case for meaningful intensive care patient and relative involvement and how this can be achieved.

Why Involve Former Intensive Care Patients and Relatives?

The short answer is because we have a perspective that no amount of training or clinical experience can provide. We know what it is like to have intensive care treatment and the profound effect that it has. Any strategic or research project that does not involve patients and relatives will be lacking this depth of understanding, and will be poorer for it. Healthcare professionals can have a good awareness of what patients and relatives go through, and this is especially so if they have spent time talking to both about their experiences, but only from being there can you truly know what it means to be critically ill. And all initiatives, whether research or strategic planning, are about improving intensive care treatment, so how can former patients and relatives ***not*** be asked to contribute towards this?

The many unique elements to being critically ill mean it is not comparable to any other type of illness or hospital stay. If you require emergency ICU admission, you have no time to prepare or understand what will happen to you. You often cannot engage in your treatment or discuss with the medical staff what is required and why. Additionally, a complete inability to make sense of your surroundings can cause you profound distress. Critically ill patients can experience:

- Partial awareness when under light sedation;
- Delirium;
- Paranoia;
- Confusion, disorientation and an inability to retain information;
- Inability to communicate;
- Alien environment;
- Lack of real sleep.

Patients often cannot understand and process what is happening to them at the time, and this leaves a legacy of psychological distress, which needs support and rehabilitation afterwards to enable them to come to terms with it.

Relatives' experience of critical illness is different than that of the patients, but it is also deeply distressing. They feel powerless to help their family member, not knowing if they will even survive. This is combined with a desperate worry about what is going to happen in the future, and uncertainty over the care that the patient may need once discharged. For many families, critical illness brings significant changes, which may be permanent; the psychological and physical after effects may mean that the patient is unable to return to normal activities, including their work, and there is an increased care burden placed on family members. Both patients and relatives need significant support and information to help them with their recovery and to understand what has happened. Sadly, in the UK this support is often not provided.

It was the recognition of this need that inspired the founding of ICUsteps, the UK patient and relative intensive care support charity. Mo Peskett, a Senior Sister at Milton Keynes General Hospital, was responsible for the hospital's follow-up clinic and saw first-hand the after effects of intensive care treatment. In 2005 she and Peter Gibb, a former ICU patient, set up the first support group for intensive care patients and relatives in Milton Keynes. The idea was to provide patients and relatives with a place to come where people truly understood, sharing 'empathy, not sympathy', where those further along the journey of recovery could support those just beginning it. It is hard to overstate just what this means to patients and relatives in their early recovery, hearing from others who have been there and had similar experiences, learning about what helped them and that recovery after critical illness is possible.

Since that small beginning, it has been quite an extraordinary journey. We now have over twenty affiliated support groups across the country. We provide high quality information for patients and relatives, and since our information booklet *Intensive Care: a guide for patient and relatives* was first printed in 2008, we have distributed 150,000 copies to UK hospitals. It is also available in sixteen languages on our website, and we have received requests from numerous countries around the world for permission to adapt it for their use. In 2013 we held our first conference, attended by over two hundred healthcare professionals and last year our website had 21,000 visitors. We are proud of our achievements, not least because we have no paid staff; our charity is run entirely by patient, relative and healthcare professional volunteers.

Although the scope of our work has changed over the last ten years, our aims have stayed true to our original principles, which are to:

- support patients and relatives affected by critical illness;
- promote recognition of the physical and psychological consequences of critical illness through education of the medical profession and the general public; and
- encourage research into treatment and the prevention of these issues.

The secret of our success is not only that we identified an unmet need, but also because our work is a true partnership between patients and relatives and critical care healthcare profes-

sionals. As patients and relatives, we have immeasurable respect for intensive care staff and their skill and dedication that saved our lives. We also know that our personal experiences provide a unique perspective to strategic work to improve the care and treatment for future patients. As an ICU patient, you have no voice (you are often unable to communicate and are confused), so many patients are therefore unable to contribute to their care and express their wishes while in intensive care. This is why it is so vital that the voices of former patients and relatives are heard at all levels to help fill this gap.

How Can You Involve Patients and Relatives?

There are many ways to do this, but there is a caveat to be added first. Not all patients and relatives want to, or are able to contribute after their critical illness. Especially in early recovery, many are deeply distressed, and may want to cope by not thinking about their critical illness. Even many years later, they may feel unable to participate in projects that revive such distressing memories. Some patients also suffer cognitive impairment from their illness, and find it hard to read and process complex information.

> **"It is now time for meaningful patient and relative involvement to be the norm, not the exception"**

Despite these difficulties, some who have survived critical illness want to put their experiences to good use to try and help those yet to become critically ill. It is therefore important that the opportunities to contribute are provided, but there must be no compulsion to help. Additionally, patients and relatives have different skills depending on their previous experiences, and not all will be interested or will be able to participate at a strategic level, so it is important that different levels of involvement are offered, and that training and support is available to enable participation. Below are some ideas about the ways that patients and relatives could be involved:

- **Local feedback: Ask about quality of treatment provided in individual units**
  Provide the opportunity for patients and relatives to feed back to the intensive care unit about their treatment and the care they received. Many hospitals do not do this, and it means intensive care professionals miss the opportunity of dialogue and improving care for future patients. Unlike other types of hospital treatment, ICU patients and relatives are often unable to discuss their experience while they are in the critical care unit, and both may need time to reflect and understand what happened to them, so a mechanism for contacting them afterwards is required. This could happen via the critical care follow-up service, or by a paper or telephone survey. Not all patients and relatives will want to engage in this way, but it is vital that they are offered the opportunity to do so.
- **Patient and relative talks**
  These are a very powerful training tool for healthcare professionals. Asking patients and relatives to talk about their experiences can significantly increase staff understanding about how best to care for intensive care patients as well as improve awareness of the legacy and impact of critical illness.
- **Strategic participation in service planning**
  The UK has made good progress in the last ten years in improving the engagement of patients and relatives, and there are areas of good practice. For example the National Institute for Health and Care Excellence (NICE) has two patient representatives for the development of all clinical guidelines, and the National Institute for Health Research (NIHR) has two lay members on its research funding boards. Patient and relative trustees from ICUsteps have been involved with the development of three NICE Clinical Guidelines (National Institute for Health and Care Excellence 2007; 2009; 2016), the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) investigation into sepsis, *Just Say Sepsis* (Goodwin et al. 2015), and the executive board of the National Outreach Forum; National Health Service (NHS) England (through the Critical Care Clinical Reference Group), the patient and relative group of the Intensive Care Society and the Critical Care Leadership Forum. We have also commented on numerous documents, including the *Guidelines for the Provision of Intensive Care Services* (GPICS) (Faculty of Intensive Care Medicine and Intensive Care Society 2015) and the *National Competency Framework for Adult Critical Care Nurses* (Critical Care Network-National Nurse Leads 2015). Involving patients and relatives at this level of strategic planning brings a new perspective to the process, but also ensures that the end result will be relevant for future patients.
- **Research Management**
  It is now acknowledged that engaging former ICU patients and relatives in research is extremely valuable. Only in that way can we be sure that the research is both acceptable and relevant to the end user and worth the considerable investment of time and money. Again, there has been good progress in the UK with one of the main funders, the National Institute of Health Research, recognising and encouraging public and patient involvement. However, there can still be a tendency for some researchers to make this a 'tick box' exercise rather than a meaningful one. Yet involving patients and relatives as part of the research team brings significant benefits to good quality research. They ensure that:
  - the research question has meaning for intensive care patients/relatives;
  - the outcomes tested are relevant;
  - the research team is sensitive to areas that may cause participants on the trial distress, and can work towards ways to mitigate these;
  - that the researchers know the reality of ICU treatment for patients and relatives and can shape their study accordingly;
  - a different perspective is brought to the project.

There are various points that may be helpful when thinking about engaging patients and relatives in research. Many of these are also relevant for effective patient and relative participation in areas other than research too:

1) Start Early

Meaningful public and patient involvement (PPI) does not come from making a token gesture just before the funding application is due in. Researchers need to engage with patients and relatives as soon as they have the idea of the research topic — well before the application is written. This ensures that PPI input makes a difference and shapes the proposal.

2) Provide Funding

Allow money in the budget for the time given

by patients and relatives, as well as travel and subsistence expenses. PPI representatives should not be expected to contribute their time voluntarily, because this discriminates against those who cannot afford to do so. Participating can mean loss of earnings, or having to pay for childcare or for other types of care, and therefore a contribution should be paid for their time.

3) Provide Training and Development

Offer training and development opportunities to ensure that patients and relatives can fully participate. Medical research is an unknown world to many members of the public. The jargon can be off-putting and the processes unclear. Training can demystify research, as well as help patient representatives to fully participate and benefit from their involvement. This does not have to be on a formal training course, but can be from a member of the research team who is responsible for support and mentoring.

4) Enable Participation

Patients and relatives have different backgrounds and experiences. Some may find it daunting to participate in focus groups or research board meetings. It is vital that the chairperson is sensitive to these issues, that they ensure that medical jargon/abbreviations are not used during the meeting, that the lay members feel comfortable, and that they give plenty of opportunity for questions to be asked.

5) Be Sensitive to How PPI Members May Feel

Former ICU patients and relatives may find it difficult to discuss some aspects of intensive care treatment as it may bring back distressing memories.

There are also other ways for patients and relatives to be involved with research. In the UK the James Lind Alliance (jla.nihr.ac.uk) helps Priority Setting Partnerships work with patients, carers and health professionals to identify gaps in evidence and agree jointly on the priority topics for research. They are also facilitating this process in other countries such as the Netherlands and Canada. An Intensive Care Priority Setting Partnership has recently been completed, which has produced the top ten areas for research, details of which can be found at jla.nihr.ac.uk/priority-setting-partnerships/intensive-care-top-ten.

There are numerous common themes amongst the experiences of intensive care patients and relatives, but there are many individual experiences too, some of which will not necessarily be representative of standard practice. This is why it is important that patient involvement is not tokenistic and that having one representative does not presume coverage of all issues. It is important to engage as many patients and relatives as possible.

So how can you access patient and relative help?

- Find out what PPI groups are already established in your local area – universities and hospitals may have patient and relative groups that can help.
- If your hospital provides ICU follow-up support, the lead nurse may know of patients and relatives who might like to be involved.
- Consider forming a long-term PPI intensive care research group, in collaboration with other researchers, which meets to discuss new projects and asks for feedback. Requests for new members could be advertised on hospital noticeboards.
- Engage with charities and special interest health groups.

Conclusion

Patient and relative involvement in many areas of healthcare has made significant progress in the last decade, but there is still more to be done. There are examples of good practice, but it is now time for meaningful involvement to be the norm, not the exception. Good quality patient and public involvement takes time, especially to ensure that their participation is enabled, but it will pay dividends in ensuring that research and strategic planning will make a real and lasting difference to future intensive care patients. Patients and relatives can make a significant contribution, but don't take my word for it – ask them! ■

Catherine White is a former intensive care patient and is a Trustee and Information Manager for ICUsteps, a UK charity.

Further Information

- For more information about the work of ICUsteps, visit icusteps.org
- For information about what patients and relatives experience during ICU treatment, and ways to help, see: White C (2013) intensive care and rehabilitation — a patient's perspective. Journal of the Intensive Care Society, 14: 299-302.

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DIETITIANS IN CRITICAL CARE

A FUNDAMENTAL AND EVOLVING ROLE

Nutrition in Critical Care

Patients in the critical care setting are at risk of malnutrition (Heyland et al. 2011). The provision of nutrition support (enteral or parenteral) to critically ill patients is vital, but achieving the optimum quantity and balance is a contentious topic. There are two major and contradictory perspectives with respect to how much to feed critically ill patients. The first maintains that overfeeding is potentially harmful in the early phase (Casaer et al. 2011; 2013), and argues for permissive underfeeding (Arabi et al. 2015). The other argues that critically ill patients are underfed, and that the resultant kilocalorie and protein deficit results in poor outcomes, such as an increase in infections, longer ICU and hospital stays (Alberda et al. 2009; Dvir et al. 2006; Villet et al. 2005). Understanding the safety of different routes of feeding has been contentious, as historically it has been believed that utilising the gastrointestinal tract is safer than intravenous feeding (Taylor et al. 2016). This approach can limit the options and quantity of nutrition provided. The CALORIES trial (Harvey et al. 2014), the largest ICU feeding trial in the United Kingdom, demonstrated that, among adults with an unplanned ICU admission for whom early nutritional support could be provided through either the parenteral or the enteral route, there was no significant difference in mortality and infection rates at 30 days. This has a dramatic impact on patient care, as the focus can now be on how much nutrition support is optimal, with the knowledge that nutrition support can be safely delivered by either or both routes and thus achieve the target feeding rates. The problem of the optimum target for energy and protein intake, together with patient selection, still remains and needs to be urgently resolved.

Whilst feeding protocols have long been standard practice on the ICU, evidence continually suggests that their use in isolation is not sufficient to prevent nutritional deficits and thus individualised nutrition support is recommended (Heidegger 2013). This may be in the form of supplemental parenteral nutrition or post-pyloric feeding, which require careful review to avoid complications. Even with the recognition of the importance of nutrition in critically ill patients and the use of protocols to promote nutritional care, a difference between knowledge and actual practice exists (Alberda et al. 2009; Heyland et al. 2004; 2014). On average critically ill patients only receive approximately 60% of calories and 57% of protein prescribed (Alberda et al. 2009; Heyland et al. 2014), with the majority of patients failing to meet the standard of at least 80% of energy targets.

A multiprofessional approach to the treatment of critically ill patients is required to provide optimal nutritional care. The critical care dietitian is the principal professional who is best placed to provide nutritional advice to the multidisciplinary team on the optimal way to manage the nutritional needs of critically ill patients (Masterson and Baudouin 2015). They have a solid science-based educational background, informed by current evidence, and are therefore perfectly positioned to be able to evaluate and advise on the complex relationship between critical illness and nutritional status.

> **"...growing evidence to suggest the critical care dietitian is an essential member of the ICU team"**

Dietitians Improve Nutritional Management of Critically Ill Patients

Over the last 20 years, the interest in nutrition support as a therapeutic intervention has increased, thus leading to the requirement for more skilled dietitians working in critical care. Evidence is emerging that nutritional care is better provided and superior patient outcome achieved, when a critical care dietitian is involved in the multidisciplinary team (Doig et al. 2008; Braga et al. 2006). Analysis from the International Nutrition Survey continually shows a direct correlation between total amount of funded dietitians in critical care, the enhanced provision of nutrition support and earlier initiation of enteral nutrition (Heyland et al. 2010; 2011). The presence of a critical care dietitian was associated with better performance in terms of compliance with guidelines, providing at least 80% of target energy, the use of enteral nutrition, initiating enteral nutrition within 24 hours and the use of strategies to optimise delivery (Heyland et al. 2010). The combination of a dedicated ICU dietitian and an enteral feeding protocol was required to increase energy provision, increase the use of combined feeding methods to achieve targets and reduce inappropriate use of parenteral nutrition (Sogel et al. 2012). Braga et al. (2006) showed that patients had a significantly shorter length of stay when they received enteral nutrition according to the advice of a critical care dietitian. These studies clearly support the role of dietitian as a key contributor to the nutritional care of critically ill patients.

Varied Roles of the Critical Care Dietitian

The critical care dietitian has the highly developed knowledge, skills and expertise within the field of critical care to manage the complex

nutritional issues observed in these patients. Provision of nutrition support to ICU patients is complicated, and not all patients will benefit to the same degree (Alberda et al. 2009). The critical care dietitian is best placed to identify those at nutritional risk and those who are more likely to suffer harm if underfed. They will assess and take account of the many factors influencing the nutrition support treatment plan. These include assessing nutritional risk, age, and the degree of inflammation, number of organ failures, comorbidities, projected length of stay and gastrointestinal function. Critical care treatment modalities also need to be considered. For example, continuous renal replacement therapy, as it is associated with a significant amino acid loss (Honore et al. 2013) and the sedation agent propofol, which can contribute significant calories (Taylor et al. 2005). Patients with malnutrition on admission to ICU have a significant increase in 30- and 90-day mortality (Mogensen et al. 2015). The critical care dietitian effectively identifies patients who are malnourished and implements appropriate nutritional treatment plans.

The critical care dietitian is not only fundamental to the successful nutritional management of patients, but also leads on promoting the benefits of good nutritional care to the ICU team. This involves the development and implementation of evidence-based guidelines and protocols, as well as being central to the provision of teaching and education for clinicians, nurses and allied health professionals. As a key member of the multidisciplinary team, they will contribute to consultant-led ward rounds, advising on the most appropriate evidence-based nutritional treatment plans, setting nutritional goals and providing ongoing monitoring and support (Heyland 2010). They are a useful knowledge repository for junior doctors on electrolyte replacement, prokinetic agents, bowel management and feeding complications. As a core member of the ICU team, they will contribute to the ICU quality improvement agenda, e.g. developing fasting guidelines to limit unnecessary enteral feed interruptions and reducing inappropriate parenteral nutrition (PN) prescribing. Suitably skilled and experienced ICU dietitians will undertake extended scope practitioner roles, including inserting a variety of feeding tubes, using ultrasound techniques to track muscle wasting and indirect calorimetry to determine individualised energy needs (Bear et al. 2015; Taylor et al. 2010). ICU dietitians regularly participate in audit to ensure the effectiveness of nutritional protocols (Segaran et al. 2015; Wandrag et al. 2011) in addition to undertaking research activities such as PhD fellowships and participating as key authors in large multicentre nutritional trials (Harvey et al. 2014). Leading senior critical care dietitians are helping shape

the evidence base for critical care nutrition by authoring international nutrition support guidelines (Dhaliwal et al. 2014; Taylor et al. 2016). The increase in dietitians as authors from one in 2009 to five in the new 2016 Society of Critical Care Medicine guidelines (Taylor et al. 2016) reinforces the recognised value of critical care dietitians.

Future for Dietitians in Critical Care

Historically, dietitians have not been adequately funded in adult intensive care units and thus input has been limited. A survey of UK practices demonstrated serious limitations in dietetic services in critical care units. No unit actually achieved the national guidance for funded dietitians (whole-time equivalents) and the staff bandings were inconsistent (Windle 2007). This situation is also seen in adult Australian and New Zealand intensive care units, where only 25% of units had formal provision for weekly dietetic hours (Ferrie and Allman-Farinelli 2011). It is hoped that the 2015 UK *Guidelines for the Provision of Intensive Care Services* (GPICS), will help to rectify this situation (Faculty of Intensive Care Medicine and Intensive Care Society 2015). The role of the dietitian was recognised as an integral part of critical care services, with its own standalone chapter. The chapter showcases the work, roles and clinical input, including recommendations for a dedicated lead ICU dietitian, who practises at an advanced level and is suitably experienced. These UK national guidelines are already being used to assist in obtaining funding for the correct staffing levels for dietitians in critical care.

For the dietitian to significantly improve the ICU teams' capacity to implement and deliver prompt and appropriate nutrition support, adequate funding is required to ensure consistent and established dietetic input. For the dietitian to influence nutritional practices, they need to be present on the ICU and participate when important decisions are being made, such as during ward rounds, handovers, multidisciplinary team (MDT) meetings and clinical discussions with visiting teams. Having clinical privileges such as automatic referral, ability to order oral, enteral and parenteral nutrition and ordering of relevant laboratory tests combined with attendance on MDT ward rounds all are influential with increasing the dietetic profile, and establishing ICU involvement (Ferrie AND Allman-Farinelli 2011). In the UK, Health and Care Professions Council (HCPC)-registered dietitians, who are working at an advanced level, have recently gained supplementary prescribing rights. It is anticipated that the critical care dietitian will be perfectly positioned to take on the supplementary prescribing of parenteral nutrition. Most are already formulating parenteral nutrition regimens on ICU, assessing macro and micro requirements to ensure patients are neither over- nor underfed. They also provide in-depth monitoring and management of complications. Skilled advanced practice critical care dietitians should be accountable for their own parenteral nutrition prescribing, rather than relying on junior doctors to sign off prescriptions for patients that the doctors have not nutritionally assessed.

For a motivated dietitian, ICU is an exciting place to work, offering many opportunities. The extra effort put in by the critical care dietitian to gain the trust and respect from ICU team members will be rewarded with a stimulating and fulfilling career. There is growing evidence to suggest the critical care dietitian is an essential member of the ICU team. ■

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A LIBRARIAN IN THE CRITICAL CARE TEAM

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Knowledge about current research evidence is required by clinicians in order to practise safe and effective care. The health librarian occupies a unique position between knowledge resources and knowledge consumers. As such, the librarian is perfectly poised to channel accurate, reliable knowledge into the hands of the healthcare team, who can then confidently apply evidence-based decisions.

Traditionally, the library has been the domain of the doctor studying for examinations or the nurse borrowing books for academic study. In the UK health libraries are becoming anything but traditional; they provide access to the best clinical evidence and offer high-quality information consultancy services that support the key functions of an evolving National Health Service (NHS) (Health Education England 2015). Librarians possess specialised skills in searching the available evidence and presenting it in a digestible format to busy clinicians and managers to help them make informed decisions about patient care, support guideline development, and bridge the gap between research and practice (Brettle et al. 2010). Librarians are casting off their ties to the library space and venturing out into clinical areas, taking knowledge and information to the frontline, where it is needed the most (Harrison 2009).

At Wirral University Teaching Hospital NHS Foundation Trust (WUTH), the critical care team employs the expertise of a librarian to ensure that decisions about patients are made utilising the best available knowledge. The initiative has been so effective that the team is embarking on a funded research study to explore the feasibility and value of the librarian as a 'knowledge mobiliser'.

Background

The drive for evidence-based practice has been inherent in the NHS for many years, emerging from the principles of high-quality and patient-centred care sanctioned in the NHS Constitution (Department of Health 2012). Within the pressured environment of critical care, clinicians can experience several barriers to evidence-based practice, including information overload, shortage of time, lack of searching skills and limited access to information technology in a ward setting (Flynn 2010; Lappa 2005). Having easy access to the best evidence in the right place, at the right time, is an important first step in evidence-based practice (Pronovost et al. 2008).

Health librarians are trained and experienced in conducting high-quality evidence searches on behalf of clinicians (Harrison and Sargeant 2004). Studies show that librarians can influence clinician behaviour (Urquhart et al. 2007), and contribute to a range of patient and organisational outcomes including potential cost savings (Brettle et al. 2011). For librarian support to be most effective, it should be positioned in the right place in the decision-making process. At WUTH, the ward round was identified as the place where most discussions about patient care took place. Critical care ward rounds are central to team communication, the development of patient care plans and changes in practice (Dodek and Raboud 2003). A model was developed whereby the librarian attends ward rounds as part of the multidisciplinary team.

Over a ten-month trial period the librarian attended ward round once a week and collected questions posed about the patients' condition or treatment by the team (**Table 1**). Having returned to the library the librarian undertook a search of relevant information resources. Due to time pressures, a speedy yet robust evidence search was required, so search strategies were informed by the hierarchy identified in the 5S model by Haynes et al. (2006). The 5S model encourages searchers to begin with the highest level of resource in the hierarchy, systems, before moving on to summaries, synopses, syntheses and finally, individual studies, until an acceptable answer to the question is found. Thus a range of resources were searched in order to compile a summary of any guidelines, studies or clinical recommendations relating to the question posed. The evidence summary was returned to the critical care team later that day.

Data from evaluation forms were collated and analysed at the end of the ten-month period. Respondents said that the evidence summary provided by the librarian gave them a better understanding of the treatment, improved patient management and aided treatment decisions, suggesting that the presence of the librarian makes a positive impact on clinical decision-making.

Evaluation data did also point to some areas for improvement. Questions on ward round were predominantly posed by medical staff, and it was felt that other staff groups should be encouraged to ask questions too. It was suggested that the speed of response from the librarian could be improved if a tablet or

Table 1. Examples of Questions Posed by the Critical Care Team

In critical care patients with HELLP (Haemolysis Elevated Liver enzymes and Low Platelets), what is the evidence for different management formats?
Is there a formula (other than the Parkland formula) for fluid replacement administration for patients with acute burns in critical care?
What are the causes of necrotizing fasciitis? What is the latest evidence concerning its treatment and diagnosis?

Conducting the evidence-supported ward round

(L-R Victoria Treadway, Librarian; Debbie Hughes, Critical Care Pharmacist; Sophie Harris, F2 doctor; Dr. Girendra Sadera, Consultant in Critical Care; Julie Reid, Ward Manager)

other mobile device was available for use at the bedside, rather than requiring a return trip to the library to access a computer. There was also a demand for library support in other areas of the department, for example, to support management decision-making, journal clubs and departmental meetings.

The evidence-supported ward round continued on a regular basis. Gradually the role of the librarian expanded beyond ward round, to support the departmental journal club and provide evidence to support decisions around purchasing equipment. We know through ongoing evaluation and feedback that library support has informed the development of clinical guidelines, the continuing professional development of staff and has contributed to service development.

Overall, the initiative has produced a number of positive benefits to the critical care team. The presence of the librarian enables access to knowledge and evidence at the point of need, saving time and effort. The regular visibility of the librarian prompts a questioning and learning culture within the team. Embedding library support within decision-making ensures that more clinical questions are pursued and researched by a trained information professional with experience in complex search methods. The librarian also performs an important function in compiling and summarising the relevant search results for easy absorption into patient discussions. In this context the librarian can usefully act as a valuable decision-making resource for the clinical team.

Some barriers perceived by the team included resource limitations and misconceptions about the role of a librarian. A persuasive case was made to purchase a tablet to enable quicker retrieval of information at the bedside. How the librarian might support decision-making was explained prior to each ward round to encourage the team to utilise this resource. Even so, the librarian was frequently mistaken to be a pharmacist or other team member, as the concept of a librarian in a clinical area was so novel. Time and effort to explain the concept at a management level was also important to ensure that the organisation embraced the initiative.

> **“compiling and summarising the relevant search results for easy absorption into patient discussions”**

Research Study

In 2015 WUTH successfully bid for funding from Health Education North West (HENW) to develop a research study exploring the role of the librarian as ‘knowledge mobiliser’ in critical care, based on the several years of work undertaken previously. The study will go beyond the original concept of ward round support to examine a departmental-wide approach to supporting knowledge mobilisation, including the knowledge requirements of critical care patients and families.

Knowledge mobilisation (also referred to as knowledge translation, research utilisation, knowledge utilisation, research transfer, knowledge transfer and implementation science (McKibbon et al. 2012)) is a complex concept that describes the process of enabling research evidence to be applied in practice for beneficial outcomes. In healthcare, the term knowledge mobilisation is predominantly used to describe the activities that involve moving knowledge from its producers (academic researchers, research organisations) to its users (clinicians, managers, other decision-makers and patients/families) to improve people's health.

Following consultation with critical care patients and their families, the study will also explore the role of the librarian in mobilising accurate and evidence-based patient information. Patient and public engagement undertaken at WUTH found that critical care patients and families feel that they have specific information needs, and that improving information that they are given is a priority in terms of patient experience.

A librarian is perfectly placed to adopt the role of knowledge mobiliser within a team. This study aims to build on previous work to examine the contribution of the librarian to patient care. The study is due to finish towards the end of 2016.

Next Steps

Embedded library support in critical care carries several potential benefits for healthcare, including enhanced decision-making, education provision and well-informed patients and families. To realise these benefits requires persuasion at a management level and clear explanation at department level to ensure that the concept is embraced wholeheartedly. Adequate resources and systematic evaluation of the initiative are also required in order to ensure constancy and demonstrate value respectively.

The results of the study will signal the way forward in developing the role of librarian in critical care even further. The model that is developed could potentially be one that is transferable to other clinical areas that are required to make clinical decisions in a fast-paced environment. ■

For full references, please email editorial@icu management.org, visit icu-management.org or use the article QR code.

"PUBLIOMETRICS"

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The significance of research or researchers is frequently discussed and debated, so also in the medical research field. Why do we publish? This straightforward question is often difficult to answer, at least in a simple way. As a starter we can list some reasons:

- We wish to make a difference for the outcome of our patients;
- We have an obligation to do research because of unanswered questions;
- We have to do it as part of a training programme or institutional requirement;
- We want to be "visible" in the scientific community;
- We want to get funding for future research;
- Curiosity.

In order to measure the impact of research, different methods are available. They span from subjective, personalised judgement of a total scientific contribution, as often performed in a research grant application or application to an academic position — to use of various "objective" numeric variables linked to publications. The simplest method to use is of course merely to add up the number of publications, but we all know that there is more to research than just counting numbers.

In this field there are several stakeholders, the two most important being the journals and the authors (Scientists), and instruments to measure one are not automatically suitable for the other group.

Bibliometry

Bibliometry is the scientific field devoted to the development and use of various analytic methods to study literature and authorship by using purely statistical criteria. As such there is no formal evaluation of its content, with the exception of the categorisation of research field and type of publication. Bibliometry has developed considerably over the last decades, and is used extensively both for scientific journals and researchers/authors.

Journal Impact Factor

The most known bibliometric quota is a measure of the importance of a journal, more commonly known as the *Journal Impact Factor* (JIF) or just IF (Garfield 2006). However, it is important to emphasise that this is purely a description of the journal itself, and IF is only indirectly linked to the contribution of the individual authors. The JIF is described with a number, and this number is calculated for each year using the number of citations of articles from that journal in the current year (nominator) divided by the number of published articles (from the same journal) in the previous two years (denominator).

Example

If articles from a specific journal were cited 1200 times in 2014, and that journal for 2012 and 2013 had published 400 papers, the JIF is 1200/400 = 3.0.

Hence it is easy to see that the JIF is influenced by the number of citations and the number of published items. To increase the JIF there has to be an increase in citations, or a decrease (absolute or relative) in the number of articles. This also means that two journals with the same absolute number of citations (nominator) can vary a lot with regards to their JIF according to the denominator. For example, *Intensive Care Medicine* had for 2014 an IF of 7.214 with 16128 citations, while *Critical Care Medicine* had an IF of 6.312 but with 33132 citations! Increasingly, the IF has been used to rank journals, and those with a high IF are usually perceived to be the most important ones. However, from field to field IF varies a lot, in particular within medical science. **Table 1** shows the JIF within some important medical fields and its huge variations. Only very few medical journals have an IF > 20, and they are mostly general in nature (not field-specific).

The JIF can be altered in various ways. One is to increase self-citations. An example is to use the "Year-in-review" type of publications some journals publish the following year. By citing a number of their own publications from the year before this will have an impact (small or large) on the nominator that year. The other is to have as few "citable" items as possible. A recent analysis has shown that less than 25% of all published items in some journals were citable items (McVeigh et al. 2009).

It is important to underscore that JIF was not developed to rank individual authors (Scientists). The JIF is simply the mean number of citations from a two-year period, so a JIF of 3.0 means each article (from the preceding two years) on average was cited 3 times the following year. But this average is not necessarily meaningful for the individual authors of a specific article; they can be cited more than 50 times or never, and the individual impact of these two extremes is of course very large.

Other Bibliometric Methods

Hence within bibliometry other methods have been developed to better describe the contribution of a single article, and thereby better to reflect the individual author(s). These methods should be increasingly used in this context, and not just the use of JIF in an inappropriate setting.

One of the most interesting is of course the *total number of citations* of an individual author. This means the sum of how many times his or her publications are cited. Obviously this better reflects individual performance, although this method also has its weaknesses. It could happen, for example, that in a portfolio of 100 articles and 1500 total citations, one of them was cited 500 times, and the other 99 articles 1000 times. This means that the number of citations can be heavily influenced by a few very "popular" articles, while the rest are less cited (or less "popular"). To overcome this, the so-called h-index was developed in 2005 (Hirsch 2005), and has become increasingly popular. The *h-index* is not immediately intuitive, as the definition goes like this:

> *A scientist has an index of h if h of his or her Np papers has at least h citations, and the rest (Np-h) have < h citations each.*

Put into numbers, if a scientist has an h-index of 29, this means that 29 of his or her papers

Table 1. Variations of JIF within some medical fields

Field	Number of journals	Top JIF	Lowest JIF	Top Journal
Medicine general	154	55.873	0.018	NEJM
Cardiology	123	16.503	0.117	J Am Coll Cardiol
Surgery	198	8.327	0	Ann Surg
Emergency medicine	24	4.695	0.2	Ann Emerg Med
Critical Care	27	12.996	0.438	Am J Resp Crit Care
Anaesthesiology	30	5.879	0.438	Anaesthesiology

Source: ISI Web of Knowledge [now Thomson Reuters Web of Science] wokinfo.com

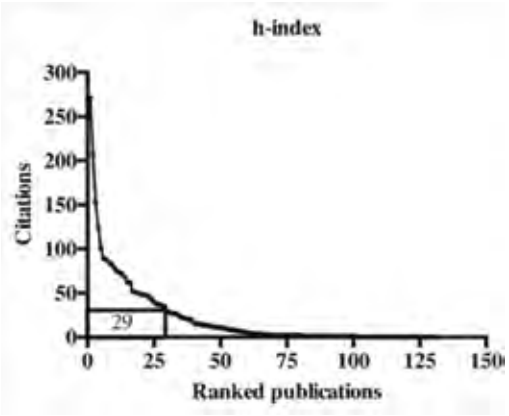

Figure 1. The h-index of an author with 130 publications and citation range from 0 to 275. 29 publication has > 29 citations.

are cited more than 29 times, and the rest ≤ 29 times (**fig. 1**). It is then understood that the higher the h-index is, the more "impact" that author has.

One advantage with the h-index is that it is more representative for the whole "production line". Outliers like a couple of highly cited publications, or some low cited ones will not substantially affect the number. In the field of anaesthesiology, it has been shown that the h-index is a good indicator for academic activity (Pagel et al. 2011).

Still, there are deficits with both total citation and the h-index with regards to individual scientists. Different databases may come up with a different h-index for the same author, and it is often found to be higher using Google Scholar than other bibliometric databases. To compare individual authors the same database must be used.

These measures do not take into account the number of authors of a single publication, nor the sequence of the individual authors; all are given equal credit. Today, not infrequently, there may be 10-20 authors or more on a single paper, and the individual contribution to the work may sometimes be difficult to see. Usually also the first and last position are considered more important. The first one as the main researcher, and the last usually the more senior or supervisor of the project. Bibliometrics to illustrate such differences are not frequently used, and often have to be retrieved manually.

Another interesting aspect is the development over time. Is the publication line increasing, decreasing or on a steady state? In order to analyse this dimension, the number of publications or citations per year must be set up, and this is sometimes done automatically in some bibliometric databases.

The Future

What will the future bring? The rapid development of web-based resources will probably alter the way we look at individual authors and scientists—based on the assumption that the significance of a publication usually is not counted in citations, but also that it is downloaded, read, and ultimately of course that its scientific and clinical findings may improve patient care. This brings bibliometrics to another dimension; we could maybe call this "publiometrics". On the web we now find portals where research and publication is displayed and discussed. ResearchGate (researchgate.com) is just one of many portals where individual scientists may gather information, and the system then calculates different metrics to describe individual performance. The system also automatically screens for new publications that can be added to the portfolio. ResearchGate tracks the popularity of your publications as "reads" (how many read/download your publication) in addition to the total citations. They have also introduced their own impact points based on a number of inputs, including downloads and web discussions. The number of downloads of an individual paper may also be found on the homepage of individual open access journals like *Critical Care*.

"The importance of a paper is also increasingly reflected in downloads and comments and likes on web-based media"

Increasingly social media like Twitter are used to distribute research and publications (engineering.twitter.com). The number of tweets may in the future also be used as a "publiometric" (Chatterjee and Biswas 2011). Several medical journals now send out tweets simultaneously with publication in order to increase awareness of the event.

Conclusion

To end this short presentation of bibliometry, it is important to realise that IF is a measure of the impact of a journal, and not suited to describe individual researchers. The latter group should be evaluated using several techniques, including the h-index, the total number of citations, citation profile with time and the place in the row of authors if applicable. The importance of a paper is also increasingly reflected in downloads and comments and likes on web-based media. ■

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CRITICAL CARE EDUCATION AND LEADERSHIP

Todd Dorman takes office as President of the Society of Critical Care Medicine (SCCM) in February 2016. He is Professor of Anesthesiology and Critical Care Medicine and Vice Chair for Critical Care Services, Department of Anesthesiology/ Critical Care Medicine; Senior Associate Dean for Education Coordination; Associate Dean for Continuing Medical Education at Johns Hopkins University School of Medicine. In addition he holds Joint Appointments in Internal Medicine, Surgery and the School of Nursing. He is a long-standing and valued member of the Editorial Board of *ICU Management & Practice.*

As you take office as President of the Society of Critical Care Medicine, what are your priorities?

I have some personal interests that I want to ensure we make progress on. These are all derived from our strategic plan, which in conjunction with our mission statement helps guide what the foci for the SCCM will be.

- For patients, the THRIVE initiative (sccm.org/Research/Quality/thrive/Pages/default.aspx) recognises that the impact of critical illness does not end at ICU discharge. It is critical that we learn what happens in our survivors so that we can facilitate their progress as well as identify opportunities to improve care during critical illness in manners that mitigate negative long-term consequences.
- The focus on sepsis in resource-limited countries is also aimed at patients and is being conducted in partnership with the European Society of Intensive Care Medicine (ESICM).
- The SCCM partnership with the Critical Care Societies Collaborative (CCSC) is focused at our own team members. We hope to advance our knowledge regarding burnout and post-traumatic stress disorder (PTSD), and thus help mitigate the occurrence of these harmful outcomes that drain our teams of experience and expertise. Interprofessional education is critical to this goal as ICUs function as integrated teams. Education by and for the team is essential to building resilience as well as for the correct execution of care in a complex environment. Interprofessional education is not simply people from different fields in the room together, but it is individuals from across the fields represented on the team interacting and learning together frequently through joint problem solving.

You recently published a paper about the implications of the U.S. Affordable Care Act for intensive care (Dogra and Dorman 2015). Please summarise your thoughts.

The Affordable Care Act will likely impact ICUs in many ways. ICUs will need to think more longitudinally about care and thus ICUs will start to think more about what happens after ICU discharge. This is but one reason why focusing at Post-Intensive Care Syndrome through the THRIVE initiative is important. Data collection and demonstration of quality outcomes will be required to negotiate reimbursements, so data-driven management strategies for the unit and the team will be important. Soft admissions will be eliminated. Clinicians will have to learn the difference between "want" and "need" and focus solely on "need" as wasted cost will not be tolerated.

What are your thoughts on how and how much clinicians from other disciplines should be involved in critical care?

Our focus should be on the competencies of the individuals. Our patients and their families deserve someone who is competent and present. We continue to have open discussions with a variety of professional societies that interface with critically ill and injured patients.

Is intensive care education fit for purpose? Is there sufficient education for the 'soft' skills intensivists need – management, team working, leadership etc.?

Presently there is little data specifically in the ICU environment. This is an area ripe for academic pursuit.

What are your top tips on maintaining a great team?

- Results at the pace of relationships;
- Taking the time to get to know the team members;
- Spending valuable time in the course of care not just in care. For instance, having lunch when on service with team members helps build the depth and breadth of the relationship;
- Running rounds in a true team fashion where everyone's opinion is truly valued is critical;
- Finally, being open to feedback is not only a marker of professionalism, but helps build trust.

You have observed that a major challenge in critical care is changing the paradigm from passive to active education models and engaging the entire team. Could you expand on that?

Most physicians were taught in a passive education style. The material is presented, and you

are merely supposed to digest it, incorporate it and change when appropriate. This approach contributes to the common belief that it takes more than 15 years for new information to highly penetrate care decision-making. We need our faculty taught to be active teachers that use active instructional designs. In addition, the ICU team functions as a team and so interprofessional education is required. Such education should use active approaches and be more about team problem solving, team involvement in simulation, etc. These approaches will lead to faster improvements in care, more durable change and more satisfied teams.

Can medical education be a value centre? How do you measure effectiveness of continuing medical education?

Continuing medical education (CME) provides value at many levels. There are now numerous critical reviews that have demonstrated the educational value of accredited CME as well as the potential for impact on patient care. Physicians have historically believed that when they finished training they were experts. In fact, when they finish training they are proficient. They can develop into an expert over the subsequent years through experience and ongoing active education. For instance, meaningful personal reflection is critical in the development of an expert. I bring this issue up, as under the historic model, CME was really there to serve as an awareness phenomenon. It has only really been in the last 5-7 years that CME has taken on the challenge of being integrated into quality and safety programmes and to academically assess its impact at the patient level. The early studies are quite promising in this regard. So where CME outcomes used to be participation rates and satisfaction scores, the outcomes that are now focused on include physician performance and patient/population outcomes. I should point out that historic approaches to things like Grand Rounds should not be expected to be associated with changes in practice or performance. Such sessions are much more about awareness of information, as they typically do not use active teaching or learning principles.

> **“Meaningful personal reflection is critical in the development of an expert”**

Could computer-assisted education be helpful in disseminating information to difficult-to-reach patients?

Mobile availability will likely be the format that reaches the most. Many resource-limited environments do not have access to standard networks, but the population does have a mobile device. Such systems can facilitate delivery of actionable information to patients and can also serve as a portal for simple data collection from the patient and/or their family. ■

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ZOOM ON TODD DORMAN

1.What are your key areas of interest and research?

The intersection of adult education, technology and clinical practice improvement.

2.What are the major challenges in your field?

Changing the paradigm from passive to active education models and engaging the entire team.

3. What is your top management tip?

Communicate, communicate, communicate.

4. What would you single out as a career highlight?

Every small victory against disease at the bedside.

5. If you had not chosen this career path you would have become a...?

Chef.

6. What are your personal interests outside of work?

Family, sports, reading and cooking.

7. Your favourite quote?

Success is the pathway not the endpoint.

CENTRE FOR RESEARCH IN INTENSIVE CARE

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The Centre for Research in Intensive Care (CRIC) was established in 2015 to provide support and services for research into intensive care, intervention and treatment (CRIC.nu). CRIC was established to maintain and improve the infrastructure obtained through the large trials conducted in Denmark, the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) (Perners et al. 2012) and Transfusion Requirements in Septic Shock (TRISS) (Holst et al. 2014) trials.

The Centre is a partnership between Danish researchers who conduct clinical trials, systematic reviews, biostatistics and health-related socio-economic analyses. Funding is from the public Innovation Fund Denmark. CRIC's mission is to provide scientific, methodological, statistical and/or management services or support to new or experienced researchers in whatever aspects of research they may pursue related to improved care and treatment of intensive care patients. CRIC's vision is to become a national service and an international collaborator for intensive care researchers.

> **"We have improved the care for ICU patients through our research and want to continue to the benefit of patients, relatives and society"**

CRIC is working for:

- transparency in research processes;
- improved public access to data and results;
- best-practice approach;
- standardised processes.

Danish ICUs are involved as partners running clinical research programmes and as trial sites in the ongoing trials. CRIC maintains an open policy, so that all Danish intensivists with a good idea for a research programme are welcome, if the programme fits the model. The model is to run clinical programmes containing a large randomised controlled trial (RCT) of frequent interventions given to ICU patients for which there are doubts about the balance between benefit and harm. The CRIC management and steering committees make the final decision on what programmes to run. Any new programme should raise the resources for itself, but CRIC staff will help with this.

Current Research Programmes

There are five clinical and non-clinical programmes taking place between 2015-2021.

Stress Ulcer Prophylaxis (SUP) in the Intensive Care Unit (SUP-ICU) (NCT02467621) (clinicaltrials.gov/ct2/show/NCT02467621)
This will assess the benefits and harms of stress ulcer prophylaxis (SUP) with proton pump inhibitors (PPI) in adult ICU patients. The research programme comprises a topical systematic review, a systematic review and meta-analysis, an international 7-day inception cohort study, an international unit evaluation and a randomised clinical trial of pantoprazole vs. placebo. The participating countries are Denmark, Norway, Finland, the Netherlands, Italy, Switzerland and the UK. The randomised trial started recruitment in January 2016 and 112 of the 3350 acutely ill ICU patients have been randomised.

Agent Intervening against Delirium in Intensive Care Unit (AID-ICU)
This will assess the benefits and harms of antipsychotics in adult patients with delirium in the ICU. First an international inception cohort study will be done to describe current use of haloperidol and other pharmacological agents for delirium in critically ill patients admitted to ICUs in Denmark, Norway, Sweden, Finland, Netherland, Switzerland, Germany, the UK, Italy, Belgium, Canada, Brazil, Spain and France. Based on the results of the cohort study and those of a systematic review with meta-analysis and trial sequential analysis, a large randomised trial will be designed to inform clinicians on the use of anti-psychotics for ICU patients with delirium.

Hypoxaemia Oxygenation Target for ICU patients (HOT-ICU)
This will assess the benefits and harms of different oxygenation targets in adult ICU patients with acute respiratory failure. The research programme comprises retrospective cohort studies, a systematic review and meta-analysis, and a large randomised clinical trial of lower vs. higher oxygenation targets in ICU patients with acute respiratory failure.

Improving meta-analyses of ICU interventions
This programme will improve the methods for meta-analysing trial data of interventions given to ICU patients including trial sequential analysis and independent patient data meta-analysis.

Improving the analyses of time-dependent data in ICU trials
This programme will improve and develop the analyses of time-dependent variables in trials of ICU patients to better understand the why, the how and the how much of interventions' effects. ■

CRIC
Centre for Research in Intensive Care

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CRITICAL CARE IN DENMARK

INTERVIEW WITH PROFESSOR INGRID EGEROD

Prof. Ingrid Egerod, RN, MSN, PhD is an active critical care researcher who has focused on the wellbeing and recovery of intensive care patients during admission and recovery. Her particular areas of interest are sedation, mechanical ventilator weaning, patient experiences, family care, ICU diaries, ICU follow-up consultations, ICU environment modifications, as well as symptoms and conditions such as pain, sleep, agitation, and delirium. She co-founded and chaired the Nordic Association for Intensive Care Nursing Research (NOFI).

What are the main challenges for critical care in Denmark?

We have the same as in many other countries. We have very good critical care but competing finances when it comes to expenses such as medications. We are fortunate to have high staffing levels, so that is not a major challenge in Denmark.

What areas of critical care practice in Denmark can other countries learn from?

Our profile in Denmark has been to take a very human approach to patient care. One thing that has been characteristic for Danish practice is that we use very little sedation (Egerod et al. 2013a)—in other countries this has been regarded as somehow 'cheating', because instead of sedating we have more staffing. But having good staffing levels means that the patient doesn't have all the complications that intubation might give later on.

I think also that we are willing to try some things because we are more autonomous in Denmark than in many other countries. The very human approach in Denmark and in the Nordic countries means we avoid physical restraints, we work a lot with the environment, we pay lots of attention to light and sound and we have dynamic lighting in most ICUs now. The human approach is a sort of 'trademark' in Denmark and Nordic countries.

You are one of the authors of an international survey on the state of critical care nursing education in Europe (Endacott et al. 2015). What is the system for critical care nursing education in Denmark?

There are positive and negative things to say about our critical care education. The positive is that it is a two-year education. The nurses have a lot of practical, hands-on experience in all areas of critical care and they end up writing a short paper. The drawback is that it's not an academic degree—it's a diploma add-on to the basic nursing education. The quality of the final paper would be better if it was part of an academic programme, but regarding the practical aspect it is a very good education, with so much exposure to all areas of critical care.

You have researched intensive care unit spousal care-giving (e.g. Ågård et al. 2015). How might this research inform practice? Is there sufficient support in Denmark for intensive care unit survivors?

We have done a lot of research on survivorship and spousal care-giving. I would say that we are not there yet—we still need to do more work. We are very aware of the importance of family for the patient who is critically ill and also that the patient's critical illness has a great impact on the family and spouses in particular. So we have follow-up groups for families, but it's not a complete systematic national programme yet. However, we are very aware that it is what we would like to provide.

What's holding it back?

A combination of lack of evidence and finances. Everything in the healthcare system is easier to get financed if there is a lot of strong evidence that it is critical. In Denmark we have very high-quality life-saving critical care, but like most other countries we have less preventive care and aftercare. We are very aware that we need more aftercare, but the problem is that the international studies on aftercare of patients and family do not have enough evidence. The weakness is that these are human reactions and human reactions are not as easy to produce a lot of hard evidence on compared to sepsis or other conditions. We still need better instruments to record and understand human response. We are still working on it.

On intensive care follow-up you have made various recommendations in your 2013 study (Egerod 2013b). Can you comment on how this will be taken forward?

We have several ongoing PhD studies that are working on different ways to help the patient and the family during the ICU stay and in

aftercare. Our big challenge is that we use the Short-Form Health Survey (SF-36) and other quality-of-life instruments that don't capture all that we are actually looking for. Therefore we are still trying to get stronger evidence by finding other ways to research this, but all our qualitative research shows that the families are very grateful for the aftercare they get. So it's getting more common that we do provide some kind of aftercare for both patients and their families.

What are the issues with qualitative research?

It's always been a problem with the field of psychology that they have had to balance between the qualitative and quantitative paradigm. It is much more difficult to predict human reactions than it is to predict things that can be measured specifically. So we are trying to combine qualitative and quantitative research methodologies. In Europe we are conducting a lot of research on intensive care delirium, because delirium is something that can be identified, treated and prevented and it has an impact on how the patients do later on. Here it is necessary to combine the methodologies to get the full picture of how we can handle this situation. It is an inherent problem when we study human reactions. One of the problems in research is that in a lot of these grant committees physicians want to give grants to basic research and don't regard patient reactions or psychological reactions as actual research, they regard it more as some kind of development work. It is more difficult to get funds for this type of research. On the other hand it doesn't take much to help the actual human being in daily life. There is a very short way from research to practice where we can actually help people, but it doesn't have the same status.

You have called delirium "the new black" (Egerod 2013). What did you mean by that?

What I meant was that all of sudden there is a lot of research of delirium. We have always had the knowledge from way back that when people had high fever, they get delirium or what we called earlier the ICU syndrome or other names. But it was not until around 2000 that Wes Ely and the team from Vanderbilt came out with the CAM-ICU to assess delirium (icudelirium.org). Once it had a name everybody recognised it here and it kind of became the 'new black' in research. More papers are coming out on delirium and it's a very important topic, because it's an issue we can do something about. We think that if we can have the patients sedated less and keep them awake then we are able to mobilise them, get them out of bed earlier and when people are out of bed earlier and they have their head up and feet down, they tend to have less much delirium, so we are starting to get to do something about it. ■

Statistics

Total population	5,619,000
Gross national income per capita (PPP international $)	44
Life expectancy at birth m/f	78/82
Probability of dying between 15 and 60 years m/f (per 1,000 population)	100/60
Total expenditure on health per capita (Intl $)	4,552
Total expenditure on health as % of GDP	10.6

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

Directory

Centre for Research in Intensive Care	cric.nu
Danish Intensive Care Database	kcks-vest.dk/kliniske-kvalitetsdatabaser/dansk-intensiv-database
Danish Society of Anaesthesia, Critical Care and Recovery Nurses	dsr.dk/fs/fs3/english
Danish Society of Intensive Care Therapy	dsit.dk
Danish Society of Anaesthesiology & Intensive Care Medicine	dasaim.dk
Danish Society for Emergency Medicine	akutmedicin.org/en.html

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AGENDA

April

7-9
12th Emirates Critical Care Conference 2016 (ECCC 2016)
Dubai, UAE
eccc-dubai.com

14-15
17th Annual Symposium on Patient Blood Management, Haemostasis and Thrombosis
Dublin, Ireland
nataonline.com

14-16
German Society of Anaesthesiology and Intensive Care 63rd Annual Meeting 2016 (DAC 2016)
Leipzig, Germany
dac2016.de

18-21
16th International Conference on Emergency Medicine (ICEM 2016)
Cape Town, South Africa
icem2016.org

28-29
13th Annual Critical Care Symposium 2016
Manchester, UK
critcaresymposium.co.uk

28-30
ESICM Regional Conference
The Art of Trauma Resuscitation
Porto, Portugal
esicm.org/events/summer-conferences

May

1-4
Brainstorming Meeting "Big Questions for the Experts"
Nice, France
intensive.org

21-24
Heart Failure 2016 & 3rd World Congress on Acute Heart Failure
Florence, Italy
escardio.org/HF2016

28-30
Euroanaesthesia 2016
London, UK
euroanaesthesia2016.esahq.org

June

1-3
Urgences 2016
Paris, France
urgences-lecongres.org

1-4
EuroELSO 2016: 5th International Congress
Glasgow, Scotland
glasgow-euroelso2016.com

4-8
8th World Congress of the World Federation of Pediatric Intensive & Critical Care Societies (PICC 2016)
Toronto, Canada
picc2016.com

13-16
SMACC DUB 2016
Dublin, Ireland
smacc.net.au

16-17
Neurosciences in Intensive Care International Symposium (NICIS 2016)
Paris, France
nicis.fr

20-21
2nd BRACE: Brain Critical Care and Emergencies Meeting
Brussels, Belgium
intensive.org

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