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VOLUME 18 - ISSUE 1 - SPRING 2018

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Luciano Gattinoni, MD

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After All, Brain Oxygenation Is What Really Matters

Andre Denault, MD, PhD, ABIM-CCM, FRCPC, FASE, FCCS

Department of Anesthesiology, Critical Care Program Montreal Heart Institute, and Centre Hospitalier de l'Université de Montréal, Université de Montréal Montreal, Quebec, CanadaAnesthesiology Mount Sinai School of Medicine Mount Sinai Hospital, New York.

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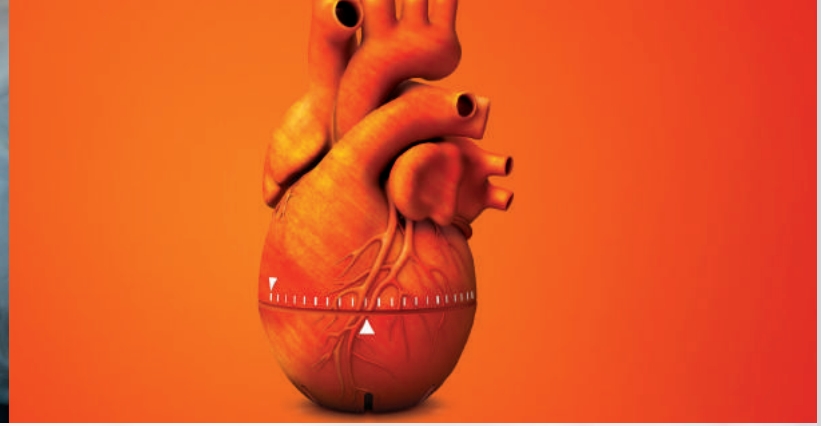

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ORION PHARMA

ICU MANAGEMENT & PRACTICE VOLUME 18 - ISSUE 1 – SPRING 2018

Multiple organ support

Interventions intended to support one organ can have unexpected implications on the patient, presenting physicians with critical decisions. These can be aided with innovative technologies and new techniques, but only if well understood. We often come across multiple organ dysfunction syndrome (MODS), with incremental degrees of physiologic derangements in individual organs, which should be seen as a continual process, requiring a harmonised, multidisciplinary approach to management.

Darryl Abrams and colleagues start us off on our Cover Story journey into multiple organ support, with their discussion on the need to understand how devices intended for support of one organ can have an indirect impact on other organs—an important consideration given renewed interest in novel extracorporeal technologies as a means of supporting individual organ failures. As devices evolve to offer simultaneous support for multiple organ failure, it will be important to emphasise a multidisciplinary approach at centres capable of performing both extracorporeal and advanced non-extracorporeal management strategies.

This takes us to the next article in our Cover Story from Claudio Ronco and associates. They describe the concept of extracorporeal organ support (ECOS) for treatment of combined organ dysfunction in critical illness and suggest creation of a new generation of ECOS equipment with integrated features to avoid artificial organ negative cross-talk.

Darryl Abrams and cohorts then take us to the topic of chronic respiratory dialysis, providing us with a focus on the potential of extracorporeal carbon dioxide removal techniques to manage chronic hypercapnic respiratory failure. From here, we move on to devices for the heart, with Nadia Aissaoui and colleagues providing guidance for understanding the physiology of mechanical assist devices, their functioning, potential complications and their management.

In our Series section on gases, Luis Morales-Quinteros and cohorts provide a focus on the potent effects that carbon dioxide exerts on lung biology, which could be particularly relevant in patients with acute respiratory distress syndrome (ARDS).

Moving on to our Matrix, we start with an article from Velma Herwanto and associates, which provides an overview of the recent advances in the diagnosis and treatment of immune system dysfunction in sepsis. Following this, Raimund Helbok and Ronny Beer review the evidence supporting the use of hypothermia in neurocritical care patients beyond care after cardiac arrest. Here, they look at ongoing clinical trials of targeted temperature management for neurocritical care and provide some thoughts for designing future studies.

Shashank Patil and Fiqry Fadhlillah then provide us with a review of invasive and noninvasive devices that can be used to monitor intracranial pressure, following which Isabel Gonzalez provides a brief report on complications of decompressive craniectomy in neurological emergencies. Finally, Fiona Howroyd details a multidisciplinary collaboration to develop a communication device for tracheostomy patients in the intensive care unit, moving from patient ideas and innovation through to readiness for clinical trial.

In our Management section, Lia Losonczy and colleagues provide us with a description of the framework they used to create a specialised unit, which operates with emergency department flow, and facilitates timely transfers of critically ill patients. Following this, Andrej Michalsen looks at variation in end-of-life care (EOLC), and asks whether we need yet another standard operating procedure, or whether a roadmap would be better to harmonise EOLC across institutions and, perhaps, healthcare systems. Miriam Poggioli and colleagues then engage in a brief discussion on the importance and the state of the art of simulation in anaesthesia and intensive care medicine, after which John Dale-Skinner moves our focus onto the practicalities of being an expert witness and what qualities are needed to succeed in this important role.

Our next article is from Karen Jones, who discusses the role of the chaplain as a resource for ethically competent support and compassionate caring for patients. After this, John Welch and colleagues present us with a focus on the joining of the International Society for Rapid Response Systems with the Patient Safety Congress in July 2018 to develop new approaches to managing patients at risk of deterioration.

In our Interview section, Jukka Takala discusses withus how to provide better intensive care with a systems approach and individualised care, followed by an interview with Elie Azoulay with a focus on whether we can do a better job caring for critically ill immunocompromised patients.

I hope you find this issue stimulating. If you would like to get in touch with me, please feel free to email me at JLVincent@icu-management.org.

Jean-Louis Vincent

Jean-Louis Vincent
Editor-in-Chief
ICU Management & Practice Professor
Department of Intensive Care
Erasme Hospital / Free University of Brussels
Brussels, Belgium
JLVincent@icu-management.org
@ICU_Management

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Route de Lennik, 808, B-1070 Brussels, Belgium
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MANAGEMENT

INTERVIEWS

Mindray launches BeneVision N1 for uninterrupted monitoring during intra and out-of-hospital patient transport

Mindray announces the release of the BeneVision N1 Patient Monitor. Designed for the varying demands of both intra and out-of-hospital patient transport, the BeneVision N1 provides a steadfast and versatile solution that integrates seamlessly into the BeneVision Patient Monitoring Solution with maximum mobility, patient-centric data continuity and streamlined workflow.

In compliance with out-of-hospital patient transport standards such as EN1789, EN13718-1, IEC60601-1-12 and U.S. military standards, N1 is a highly competent solution for various out-of-hospital transport settings both on land and in air.

The BeneVision N1 combines state-of-the-art design, innovative technology with a clinically tested ease-of-use workflow, all while maintaining patient data continuity. Weighing less than 1kg, the palm-sized monitor provides clear viewing from all angles with HD display touchscreen and streamlined workflow with intuitive operation.

With Platinum Multi-parameter Platform, the BeneVision N1's enhanced data analysis greatly improves parameters' accuracy and anti-interference ability. Its fully integrated sidestream CO_2 module monitors the patient's breathing situation by connecting with the sampling line directly, freeing caregivers from the shackles of expanding external modules for transport.

The BeneVision adapts to the clinical needs across the hospital from a plug-and-play module, to transport, to a stand-alone bedside monitor. It can be connected into the BeneVision N-Series bedside monitor as a module, or function as an independent bedside monitor.

The connectivity capabilities the BeneVision N1 enable it to follow a patient throughout the entire care process, ensuring data continuity for patient-centric monitoring, thereby improving overall information management efficiency.

Integrating Mindray's latest monitoring technological innovations to address clinical needs, the BeneVision N1 is designed to provide caregivers and hospitals with more value and efficiency. With its release, Mindray is set to continue the pioneering position in patient transport monitoring solutions and proven success of its previous BeneView T1 transport monitor, which has been widely acknowledged by the market. ■

Out with the saline?

Reduced use linked to better outcomes

Two companion studies have shown that use of saline as intravenous fluid therapy, compared to crystalloids, was associated with poor survival and increased risk of kidney complications.

Matthew Semler, MD, MSc, assistant professor of Medicine at Vanderbilt University School of Medicine, told *ICU Management & Practice* in an email: "Because saline and balanced fluids are similar in cost and use of saline is based on historical practice and not scientific evidence, the results of these two large, randomised trials both showing the same benefit in patient outcomes with balanced crystalloids rather than saline may be sufficient evidence to change practice for many clinicians".

The research examined over 15,000 intensive care patients and over 13,000 emergency department patients, in pragmatic cluster randomised multiple crossover trials. Patients were assigned to receive saline (0.9% sodium chloride) or balanced fluids (lactated Ringer's solution or Plasma-Lyte A) if they required intravenous fluid. The primary outcome was a major adverse kidney event within 30 days.

Semler said the pragmatic trial aimed to answer the research question while keeping patient care during the trial as similar as possible to patient care outside of a study setting. "This improves the ease with which the study findings are applied to clinical practice. By comparing balanced fluids to saline without blinding clinicians, the trials provide an estimate of the effect of the fluids on outcomes that translates easily into clinical care", he said.

In the critically ill patient group, of 7942 patients in the balanced fluids group, 1139 (14.3%) had a major adverse kidney event. In the saline group 1211 of 7860 patients (15.4%) had an adverse kidney event. The incidence of new renal replacement therapy was 2.5% and 2.9% respectively, and the incidence of persistent renal dysfunction as 6.4% and 6.6% respectively. In septic patients, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline. In the study comparing fluids in non-critically ill patients, balanced crystalloids did not result in shorter time to hospital discharge than saline, but did result in lower incidence of the composite of death, new renal replacement therapy and persistent renal dysfunction. ■

References

Self WH, Semler MW, Wanderer JP et al; SALT-ED Investigators (2018) Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med, 378(9): 819-28.

Semler MW, Self WH, Wanderer JP et al.; SMART Investigators and the Pragmatic Critical Care Research Group (2018) Balanced crystalloids versus saline in critically ill adults. N Engl J Med, 378(9): 829-39.

ICU delirium a distinct indicator of acute brain injury

More than half of ICU patients in a new study experienced delirium for long periods during their stay. Sedative-associated delirium was most common, while longer periods of hypoxic delirium and unclassified delirium were associated with worse cognitive function at follow-up one year after hospital discharge.

Patients were assessed for delirium while in the ICU twice a day using the Confusion-Assessment Method-ICU (CAM-ICU) and the Richmond Agitation-Sedation Scale (RASS) and once a day outside the ICU. The delirium phenotypes were classified according to the presence of hypoxia, sepsis, sedative exposure, or metabolic (eg, renal or hepatic) dysfunction, which were not mutually exclusive.

A total of 1040 patients with respiratory failure or septic or cardiogenic shock were included. Seventy-one percent of participants experienced delirium at least once during their stay, and delirium occurred on 31% of all 13434 participant days. In the 4187 days of delirium, one delirium phenotype was present during 1355 days (32%), two phenotypes present during 1213 days (29%), three during 1231 days (29%), and four were present during 388 days (9%). More than half of participants who experienced delirium had hypoxic, septic, or sedative-associated delirium at some time during the study; metabolic and unclassified delirium occurred less often.

Researchers assessed 564 (80%) patients at 3-month follow-up, and 471 (75%) at 1-year follow-up, to assess executive function. Longer periods of multiple delirium subcategories predicted worse cognitive decline after one year following hospital discharge. Metabolic delirium was the only phenotype that didn't affect long-term cognitive decline, after adjusting for age, severity of illness, doses of sedating medications and other factors.

Lead author Timothy Girard, MD, MSCI, associate professor of critical care medicine, Pitt School of Medicine, said in an email to *ICU Management & Practice*: "Based on this study, intensivists should monitor ICU patients for delirium and view delirium in the setting of sedation, hypoxia, and/or sepsis as red flags indicating high risk for long-term cognitive impairment. When treating a patient with sedative-associated, hypoxic, or septic delirium, they should work to identify and reduce potential risk factors, especially those that are iatrogenic and modifiable, e.g., sedation." He advised that when patients are discharged after a critical illness, those who experienced prolonged periods of sedative-associated, hypoxic, or septic delirium should be scheduled for follow-up in an ICU follow-up clinic or other setting that will facilitate assessment for cognitive impairment.

References

Girard TD, Thompson JL, Pandharipande PP et al. (2018) Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med, 6(3): 213-22.

Gut microbes protect against sepsis

New research published in *Cell Host & Microbe* suggests that gut bacteria may help in the fight against sepsis. In the study, mice were given particular microbes, which increased blood levels of immunoglobulin A (IgA) antibodies, protecting the mice against polymicrobial sepsis.

There is evidence showing that people with IgA deficiencies are more likely to succumb to sepsis. Also, previous research indicates that immunoglobulin M (IgM) antibodies quickly respond to blood-borne bacteria in sepsis and that gut microbes trigger immunoglobulin G (IgG) antibody responses that can block bacterial infection.

The current study aimed to determine whether gut microbes could trigger IgA responses that protect against sepsis. "We propose that serum IgA and IgG antibodies may play roles similar to the protective role proposed for natural IgM antibodies, with the IgA component providing a non-inflammatory mechanism for keeping invading bacteria in check," said first author Joel Wilmore of the Perelman School of Medicine at the University of Pennsylvania.

Wilmore and colleagues looked at IgA antibodies, which are readily detected in mice and humans but whose role in host protection against sepsis was unknown. The researchers found that exposing mice to a unique but natural microflora that included several members of the Proteobacteria phylum led to increases in IgA levels in the blood. Moreover, shifting the mouse gut to a Proteobacteria-rich microbiota led to IgA-mediated resistance to sepsis in mice.

When the researchers transferred blood lacking IgA into mice with sepsis, all but one animal died within two days. By contrast, mice that received blood enriched in IgA survived much longer. Taken together, the findings suggest that commensal microbes can have a substantial impact on IgA levels in the blood, resulting in protection against bacterial sepsis.

More studies are needed to further dissect the mechanism by which IgA confers protection against sepsis and explore ways to harness the specific properties of these antibodies to develop a treatment that may be applied to human disease. In the meantime, the researchers urge caution against over-interpreting the new findings.

"The study is limited by the fact that the microbiome in every person or animal is unique to some degree, and our study is in the context of the animal facility at the Perelman School of Medicine at the University of Pennsylvania," explains senior author David Allman, also at UPenn's Perelman School of Medicine. "While IgA protected mice in our study, it should not be assumed that IgA could replace standard treatments provided to patients in a clinical setting."

Reference

Wilmore JR, Gaudette BT, Allman D et al. (2018) Commensal microbes induce serum IgA responses that protect against polymicrobial sepsis. Published online in Cell Host & Microbe, February 22, 2018. DOI: 10.1016/j.chom.2018.01.005

Introduction to multiple organ support

There is a renewed interest in novel extracorporeal technologies as a means of supporting individual organ failures. An emphasis should be placed on characterising the spectrum of extracorporeal devices for various organs and understanding how devices intended for support of one organ can have an indirect or direct impact on other organs, which is particularly relevant as different extracorporeal platforms may become integrated.

Multisystem organ failure is commonly encountered in the intensive care setting, often requiring a multidisciplinary approach to management. It is increasingly being recognised that organ failures do not exist in isolation, but rather result from and have an impact on the dysfunction of other organs, mediated by haemodynamic, neurohormonal and cell signalling feedback mechanisms, an interplay that has been termed organ crosstalk (Husain-Syed et al. 2015; Husain-Syed et al. 2016; Pelosi and Rocco 2011). Common examples of this relationship between organ systems include the cardiorenal, hepatorenal and pulmonary-renal syndromes, each of which has a significant impact on the likelihood of recovery of individual organs and overall prognosis (Davenport et al. 2017; Husain-Syed et al. 2016; Malbrain et al. 2014; Nadim et al. 2012; Ronco et al. 2012; Ronco et al. 2008). Likewise, the treatment of one organ failure often directly impacts and may adversely affect another, as has been demonstrated with the direct effects of invasive mechanical ventilation on haemodynamics and the downstream effects of ventilator-induced lung injury on kidney function (Goligher et al. 2016; Husain-Syed et al. 2016; Luecke and Pelosi 2005).

The concept of extracorporeal support of organ failure is not new, with mechanical ventilation and renal replacement therapy (RRT) having been available for decades as a means of artificially supporting lung and kidney function, respectively (Bellomo et al. 2017; Neri et al. 2016). However, in light of recent technological advances, there has been a renewed interest in novel extracorporeal technologies as a means of supporting individual organ failures, such as venovenous extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) for respiratory failure, venoarterial ECMO, ventricular assist devices (VAD) and total artificial heart for cardiac failure, and artificial liver detoxification systems for hepatic failure (Abrams et al. 2014; Aissaoui et al. 2018; Brodie and Bacchetta 2011; Chiumello et al. 2017; Thompson et al. 2017; Trudzinski et al. 2016). As a result, an emphasis has been placed on characterising the spectrum of extracorporeal devices for various organs, collectively termed extracorporeal organ support (ECOS) (**Figure**) (Ranieri et al. 2017). It will be important with time to better understand how devices intended for support of one organ can have an indirect or direct impact on another organ. This becomes particularly relevant as different extracorporeal platforms may become integrated, as has already been shown to be feasible with ECMO and RRT (Fleming et al. 2012). As these devices evolve to offer simultaneous support for multiorgan failure (Ronco et al. 2015), it will be important to emphasise a multidisciplinary approach at centres with capabilities of performing both extracorporeal and advanced non-extracorporeal management strategies, which in turn may warrant particular organisational and regionalisation considerations (Abrams et al. 2018; Combes et al. 2014).

The potential for development of integrated extracorporeal platforms has significant implications for clinical outcomes. Traditionally, patients who might benefit from one form of ECOS, such as venovenous ECMO for acute respiratory distress syndrome, are often deemed to be ineligible due to severe extra-pulmonary organ dysfunction (e.g. hepatic failure). However, with multiorgan ECOS availability, such patients might be considered preferred candidates for an integrated extracorporeal approach.

> "as devices become more efficient, portable, and durable theconversation must also address the potential future role of ECOS in the management of chronic organ failure"

Importantly, the discussion of ECOS often focuses on the management of acute organ failure within an intensive care setting. However, as these devices become more efficient, portable, and durable (Cheung et al. 2015; Kischkel et al. 2017; Ronco et al. 2014; Seiler et al. 2017), the conversation must also address the potential future role of ECOS in the management of chronic organ failure, both as novel single-organ devices and applications (e.g. artificial lung, chronic respiratory dialysis) and as integrated destination device systems (e.g. VAD plus artificial lung, RRT plus extracorporeal liver assist device, etc). In both the acute and chronic setting, advances in extracorporeal technology hold the promise of these integrated systems being

Darryl Abrams
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University College of Physicians and Surgeons/ NewYork-Presbyterian Hospital
New York, USA

da2256@cumc.columbia.edu

Daniel Brodie
Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University College of Physicians and Surgeons/ NewYork-Presbyterian Hospital
New York, USA

hdb5@cumc.columbia.edu

Marco Ranieri*
Professor of Anesthesia and Critical Care
Department of Anesthesia and Intensive Care Medicine
Sapienza Universit di Roma
Policlinico Umberto I
Rome, Italy

marco.ranieri@uniroma1.it

*corresponding author

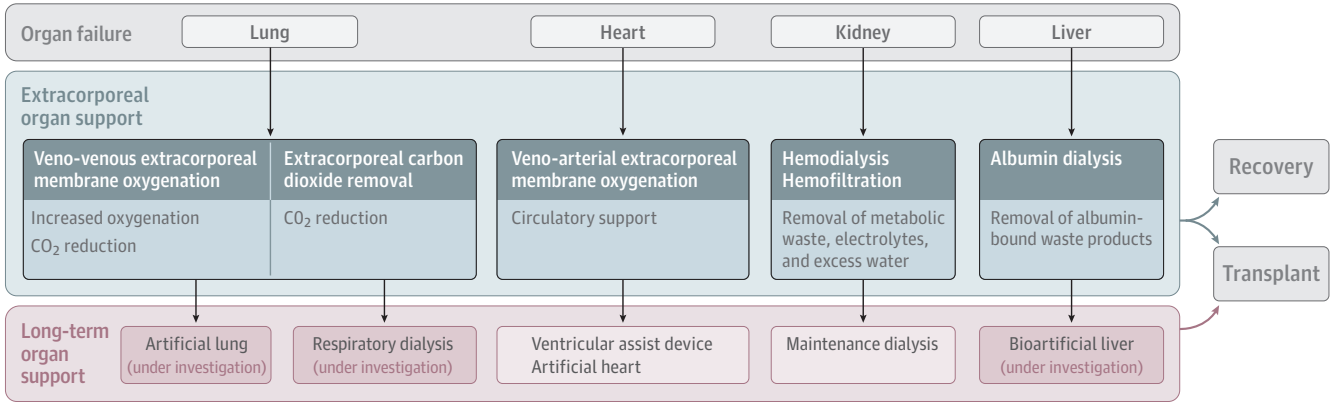

Figure. Phases of extracorporeal organ support for the lung, heart, kidney, and liver (Ranieri et al. 2017) Reprinted by permission

able to engage in artificial organ crosstalk and auto-regulation, much in the way native organs currently behave (Vincent et al. 2017).

In this issue of *ICU Management & Practice*, the authors will address the role of various ECOS systems as they currently exist, the potential for these single organ-focused systems to be integrated into multiorgan platforms, and future directions of ECOS toward long-term, multiorgan support systems, all of which will help to reframe the concept of ECOS in a new paradigm for the management of severe organ failure. ■

Conflict of interest

Daniel Brodie is currently the co-chair of the Trial Steering Committee for the VENT- AVOID trial sponsored by ALung Technologies. He was previously on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for these activities is paid to Columbia University. Darryl Abrams and Marco Ranieri declare that they have no conflict of interest.

Abbreviations

$ECCO_2R$ extracorporeal carbon dioxide removal	ECOS extracorporeal organ support
ECMO extracorporeal membrane oxygenation	RRT renal replacement therapy
	VAD ventricular assist devices

References

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

From multiple organ support therapy (MOST) to extracorporeal organ support (ECOS) in critically ill patients

The complex nature of the multiple organ dysfunction syndrome (MODS) requires an integrated supportive therapy. Native organs have a continuous crosstalk and have in common in most cases an altered composition of the blood circulating and perfusing them. In this article we describe the concept of extracorporeal organ support (ECOS) for the treatment of combined organ dysfunction in critical illness. ECOS includes all forms of therapies where blood is extracted from the body and processed in different circuits with specific devices and techniques. Simultaneous application of different devices and circuits implies possible interactions among artificial organ support systems with potentially negative consequences. We propose a multidisciplinary effort to combine all these techniques avoiding mistakes and problems and we suggest the creation of a new generation of ECOS equipment with integrated features to avoid artificial organ negative crosstalk.

Claudio Ronco*
Director
Department of Nephrology, Dialysis and Transplantation
San Bortolo Hospital
Vicenza, Italy

International Renal Research Institute
San Bortolo Hospital
Vicenza, Italy

cronco@goldnet.it

Zaccaria Ricci
Staff
Department of Cardiology and Cardiac Surgery
Pediatric Cardiac Intensive Care Unit
Bambino Ges˜ Childrenís Hospital
IRCCS
Rome, Italy

Z.ricci@libero.it

The management of critically ill patients in the ICU is progressively increasing in complexity (Kadri et al. 2017). Significant advances in care, comorbidity and advanced age of patients have led to a greater severity of illness at admission (Kaukonen et al. 2014). Simultaneous dysfunction of various organs is frequent, leading to the so-called multiple organ dysfunction/failure syndrome (MODS/MOFS) (Ziesmann and Marshall 2017).

The complex nature of multiple organ dysfunction syndrome

Several organ systems are involved in critical illness where initial impairment of one organ function is often followed by dysfunction or damage in other organs. This is especially true in the context of sepsis or other systemic disorders (Ziesmann and Marshall 2017). For example, the effect of acute kidney injury (AKI) on distant organs is now well documented (Kellum and Prowle 2018). This phenomenon may be observed with a primary injury to other single organs followed by secondary damage/dysfunction of other organs (**Figure 1**). The initial sequence of events often results in a vicious circle leading to a continuous negative organ interaction and a progressive worsening of the syndrome (Husain-Syed et al. 2015). This is typically the case in cardiorenal syndrome (CRS) where several bidirectional and temporally related heart–kidney interactions may lead to five different clinical subtypes (Ronco et al. 2008). The syndrome initiation, the primary organ involved and the mechanisms are different in nature: haemodynamic alterations and congestion, iatrogenic effect of interventions, direct toxicity of drugs or contrast media, neuro-hormonal derangements and immune-mediated/inflammatory damage (Husain-Syed et al. 2016). Nevertheless, after a significant organ crosstalk has initiated, the progressive dysfunction of both organs leads to significant worsening of the clinical picture.

> "need for next-generation ECOS machines to achieve harmonisation of components, techniques, and operations of multiple extracorporeal therapies"

Other conditions may involve acute and chronic lung disease scenarios leading to AKI or accelerated chronic kidney disease (CKD), and vice versa (Husain-Syed et al. 2016). Some of these interactions include the participation of the heart in an even more complex cardio-pulmonary-kidney crosstalk (Husain-Syed et al. 2015).

Critically ill patients may develop liver dysfunction in the context of MODS or may suffer from primary liver disorders. Liver dysfunction may become the trigger for several pathological pathways, eventually involving lungs, kidneys and brain (Siddiqui and Stravitz 2014). Combined liver and kidney dysfunction is common and described by different types of hepatorenal syndrome (HRS) (Fukazawa and Lee 2013). AKI represents a well-known complication of liver disease through different biological pathways and it is associated with increased morbidity and mortality. Renal dysfunction in cirrhosis is often functional in nature and secondary to haemodynamic derangements, cardiac dysfunction and altered plasma composition. Nevertheless, an increasing number of patients with cirrhosis may develop structural damage of the kidneys leading to a progressive deterioration of organ function (Arroyo and Jiménez 2000). In turn, once kidney function deteriorates in liver patients, a progressive worsening of the syndrome is typically observed with unfavourable outcomes.

Gut and kidney may also present reciprocal negative interactions due to primary alterations in host microbiome profile and disruption of gut barrier function leading to systemic inflammation, AKI, progression of CKD with effects on uraemic toxicity and potential increase in cardiovascular risk (Jacobs et al. 2017). On the other hand, the effects of AKI on the increased risk of bleeding and other derangements of the gastrointestinal tract have been described (Doi and Rabb 2016).

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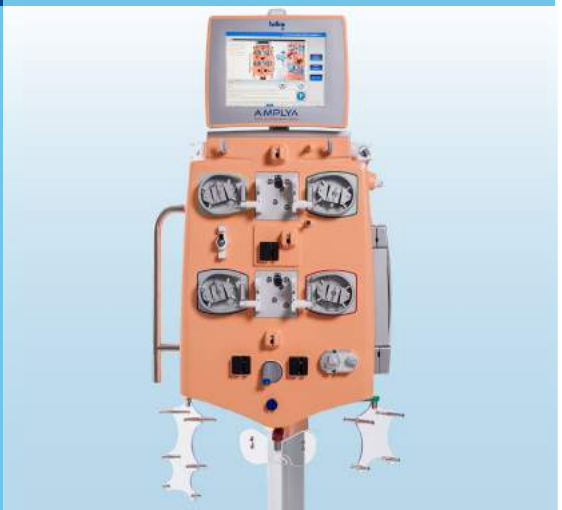

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Faeq Husain-Syed
Senior physician
Department of Internal Medicine II
Division of Pulmonology, Nephrology, and Critical Care Medicine
University Clinic Giessen and Marburg - Campus Giessen
Giessen, Germany

faeqhusain@yahoo.de

All these syndromes are often the result of a mixture of direct organ injury, secondary systemic disorders and altered tissue perfusion in different organ systems. Preexisting organ dysfunction can make the clinical picture worse (Rosenthal et al. 2018). Furthermore, primary and secondary organ injury/dysfunction results from a complex balance between individual susceptibility and exposure (insult) intensity (Agarwal et al. 2016). The interaction between these two factors is particularly evident in the case of sepsis where several organs are affected by an exaggerated and uncontrolled imbalance between the pro- and anti-inflammatory response of the host. The so-called immune-homeostasis is compromised and organ dysfunction is generally the result of altered blood perfusion and metabolism at the tissue and cellular level (Boomer et al. 2011). Although individual characteristics become less important when the intensity of exposure (insult) is overwhelming, the contribution of host response to organ injury may still be significant and precision medicine criteria should be applied for the final treatment strategy (Zieamann and Marshall 2018).

Multiple organ support therapy (MOST)

Critically ill patients with MODS require a complex and articulated therapeutic approach that includes pharmacological strategies (such as antibiotics for infection source control, circulatory and respiratory support, organ-specific drugs, correction of abnormalities of coagulation, electrolyte, acid-base, metabolism) and specific organ support systems. All these interventions should be integrated in a global strategy to support single organs and manage the combined effects of multiple organ crosstalk. In a seminal paper, we described the concept of *multiple organ support therapy* (MOST), identifying the possibility to provide simultaneous and combined support to different failing organ systems (Ronco and Bellomo 2002). MOST includes oxygenation and ventilatory support (invasive and noninvasive mechanical ventilation [MV], venovenous extracorporeal membrane oxygenation [ECMO] and extracorporeal carbon dioxide removal [$ECCO_2R$]), mechanical circulatory support (intra-aortic balloon pump, venoarterial ECMO, percutaneous and surgical ventricular assist devices [VADs] and total artificial heart), renal replacement therapy (RRT) and extracorporeal liver support (molecular adsorbent recirculating system, plasmapheresis and sorbent therapies). All these techniques are currently used in the ICU although very little is known about their interaction with native organs and other artificial organ support systems (Ronco 2006).

Extracorporeal organ support (ECOS)

Extracorporeal blood purification techniques such as haemodialysis or haemofiltration, have been used successfully for several decades to replace renal function in critically ill patients with kidney failure. New applications are today emerging for extracorporeal techniques. The experience with extracorporeal blood therapies in sepsis suggests redefining the spectrum of application, and we are today exploring the concept of *extracorporeal organ support* (ECOS) to describe all forms of therapies where blood is extracted from the body and processed in different circuits with specific devices and techniques (Ranieri et al. 2017). The principle for ECOS is that in MODS failing organs have in common the blood perfusing their tissues, and circulating blood becomes the target for specific treatments.

The idea of using extracorporeal therapies for sepsis came from the occasional observation that septic patients treated with RRT for AKI displayed a rapid and significant improvement in haemodynamics, with a reduced requirement of vasopressor support a few hours after application of the extracorporeal circulation. Further experiments demonstrated that the ultrafiltrate recovered from septic patients treated with haemofiltration and injected in healthy animals produced septic symptoms (Tetta et al. 1998). The improvement in septic manifestations in patients undergoing RRT suggested a possible reduction of circulating chemical mediators eliminated in the ultrafiltrate. The absence of significant variation in circulating levels of cytokines created some conflicting positions (Sieberth and Kierdorf 1999) that will never be resolved until a well-designed and adequately powered trial on extracorporeal therapies in sepsis in the absence of AKI is performed. Still, the question of whether mortality is the correct endpoint for such a study is wide open. Nevertheless, some hypotheses were formulated such as the

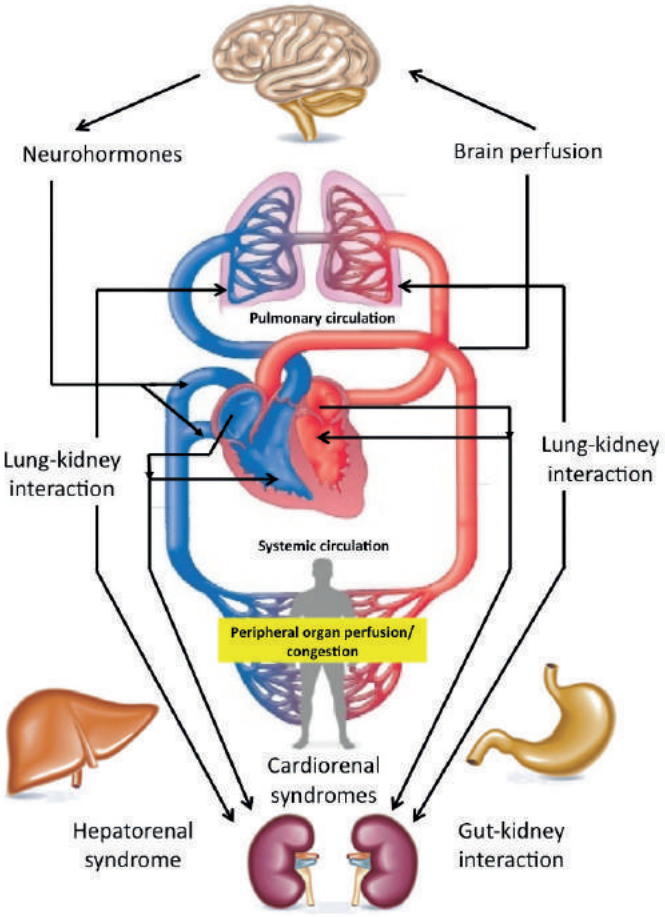

Figure 1. Schematic representation of different native organ interaction and crosstalk. The injury to one organ may result in a secondary damage/dysfunction of other organs whose compromised function activates a vicious circle and a worsening of MODS.

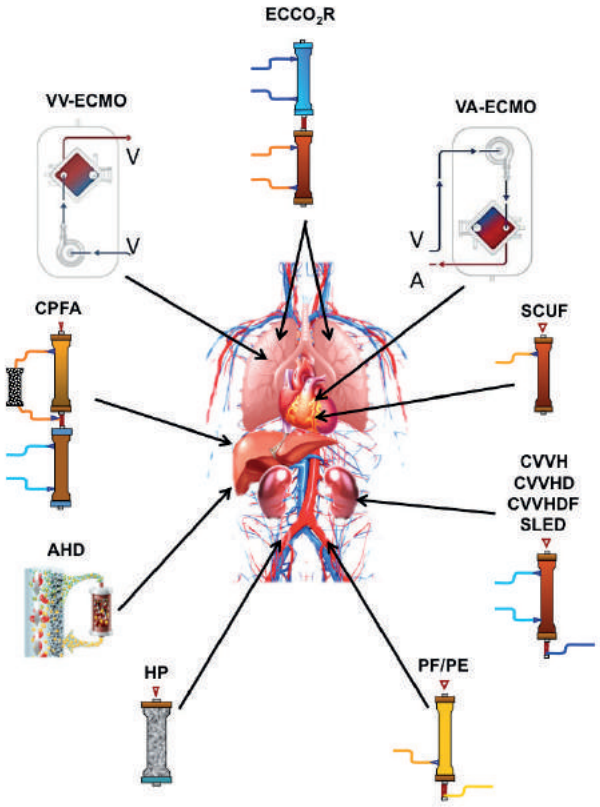

Figure 2. Schematic representation of current ECOS techniques

$ECCO_2R$ extracorporeal CO_2 removal VA-ECMO venous arterial extracorporeal membrane oxygenation SCUF slow continuous ultrafiltration CVVH continuous venovenous haemofiltration, CVVHD continuous venovenous haemodialysis CVVHDF continuous venovenous haemodiafiltration SLED sustained low efficiency haemodialysis PF plasmapheresis PE plasma exchange HP haemoperfusion AHD albumin haemodialysis CPFA continuous plasma filtration adsorption

VV-ECMO venovenous extracorporeal membrane oxygenation Minor modification of these seminal therapies have been reported in the literature but these represent the original concept

peak concentration hypothesis (Honoré et al. 2006), based on the idea that a non-selective elimination of the peaks of both pro- and anti-inflammatory mediators might contribute to a restoration of a certain degree of immune-homeostasis and to a reduction of the severe imbalance produced by the exaggerated host response to bacterial invasion. Also, a personalised approach, matching RRT intensity with the risk of albumin and amino acid, catecholamine and antibiotic loss, should be advocated to avoid jeopardising the beneficial effects of extracorporeal therapies (Bagshaw et al. 2016). The culture of this approach comes from the discipline of nephrology. For years, chronic haemodialysis has sustained thousands of lives even though a clear understanding of the molecular basis of uraemia has not been achieved yet. A similar approach can be used for sepsis and multiple organ failure where altered blood composition represents the common ground for damage/dysfunction: whatever component is in excess or defect compared to its physiological concentration in blood, it can be removed or corrected by a specific extracorporeal treatment and device. This is the basis for the application of ECOS in critically ill patients (**Figure 2**).

Kidney support

Kidney support can be provided by different intermittent and continuous blood purification techniques such as intermittent haemodialysis, slow low-efficiency dialysis, continuous venovenous haemofiltration, haemodialysis, haemodiafiltration. These techniques, based on diffusive and/or convective transport of solutes and water transport by ultrafiltration across a semipermeable membrane, allow adequate blood purification, acid-base/electrolyte correction and volume control. In the case of sepsis, such techniques are further expanded with the use of high-volume haemofiltration (HVHF), coupled plasma filtration adsorption (CPFA) and high-cut-off membrane (HCO) applications. The last two techniques are also used when liver dysfunction or rhabdomyolysis are present and large molecular size molecules are to be removed from the circulation. In the case of protein-bound solutes, albumin dialysis (AHD) has also been suggested as well as plasmapheresis (PP) or plasma exchange (PE). A special nomenclature has been created to better define the characteristics of each component of the extracorporeal circuit (Neri et al. 2016) and each specific technique (Villa et al. 2016).

Adsorption

Adsorption has been proposed as a third mechanism for solute removal from the circulation. Sorbents prepared in specific cartridges can be placed in direct contact with blood as in the case of direct haemoperfusion (HP), or used after plasma filtration (PF) from whole blood (PFAD) to avoid direct contact of platelets and white cells with the sorbent particles. After plasma is processed in the sorbent bed, blood is reconstituted and returned to the patient. HP has been used for years in case of acute intoxication, hyperbilirubinaemia and immunoadsorption. Recently, biocompatible sorbent devices have been created for endotoxin removal (polymyxin-B haemoperfusion [PMX-HP - Toray Medical Company]) or cytokine removal (cartridges for HP from Cytosorbents Corporation, Jafron Biomedical or others) in severe sepsis or septic shock.

Heart support

Heart support has been originally achieved removing the excess of fluid in the body by ultrafiltration when diuretics cannot provide adequate diuresis. The spectrum of extracorporeal techniques has today expanded to other options. Venoarterial (VA-ECMO) is used in patients with acute cardiac or circulatory failure to restore end-organ perfusion and organ function, and to bridge either to recovery, to definite cardiac support (e.g. ventricular assist devices, VADs) or heart transplantation. MODS is particularly common in patients requiring cardiac support and use of lung support and RRT may become additionally necessary (Van Dorn et al. 2018). Again VA-ECMO is part of ECOS because blood is processed outside the body while VAD, Total implantable heart, Impella® (Abiomed) or intra-aortic balloon pumps technologies belong to the MOST category but not to ECOS.

Lung support

Lung support in the context of ECOS has been traditionally identified with venovenous (VV)-ECMO. VV-ECMO is mostly used for correction of hypoxaemia refractory to lung-protective ventilation and prone position in patients with severe acute respiratory distress syndrome. The experience coming again from haemodialysis brought into clinical practice however the possibility to achieve partial lung support

with a certain removal of CO_2 from the circulation. This concept of "respiratory dialysis" has further evolved to a system where a small oxygenator is placed in series with a CVVH circuit (Romagnoli et al. 2016). The technique called $ECCO_2R$ is used as an alternative or supplement to mechanical ventilation for correction of hypercapnia, but not for blood oxygenation since the blood flows through the circuit are relatively low (350-450 ml/min). Recently, RRT in conjunction with $ECCO_2R$ has been advocated to allow "super-protective" MV settings, and reduction of vasopressor demands in patients with ARDS experiencing AKI (Allardet-Servent et al. 2015). In some cases, $ECCO_2R$ can also allow continuation of noninvasive MV, thus avoiding invasive MV.

Liver support

Liver support can be provided by albumin dialysis, plasma filtration/adsorption, plasma exchange and haemoperfusion. Not only removal of bilirubin and other protein-bound toxins can be achieved by these techniques, but also significant reduction of ammonium level can be observed during treatment. The Molecular Adsorbent Recirculating System MARS® (Gambro®), Prometheus® therapy system (Fresenius Medical) and other equipment based on cascade filtration and dialysis with albumin-based dialysate and sorbents are today available for this purpose (Faybik and Krenn 2013).

Native and artificial organ crosstalk

There is a clear need to explore crosstalk and interactions between different organ systems in the critically ill patient. The literature on complex syndromes with multiorgan involvement emphasises the need for multidisciplinary management. In these conditions, the level of multiple organ dysfunction makes MOST highly recommended or even mandatory. Frequently however, patients who display clear indication for ECMO and are undergoing such a complex therapy, may require further organ support with the addition of RRT, liver support, haemoperfusion for detoxification, or cardiac support. In these circumstances, extracorporeal support and organ replacement may become safer and more uniform if different functions are combined in a fully integrated hardware. Fluid balance, solute removal, CO_2 removal, aromatic amino acid removal, electrolyte and acid base equilibration, blood detoxification and oxygenation should be considered a continuum, where the artificial organ crosstalk is constant. Variations in CO_2 must consider the use of buffers in dialysis or the application of citrate as anticoagulant for an adequate equilibrium of acid-base. The future is likely to see the introduction of a unified hardware with special circuitry that will allow performance of all different organ support therapies on demand, simply escalating or de-escalating the complexity of the system. Thus, from ECMO and RRT, a patient may be progressively moved to $ECCO_2R$ and intermittent haemodialysis and, finally, even be discharged with organ support including chronic haemodialysis and respiratory dialysis in case of non-recovery or progression towards chronic illness.

Next generation ECOS equipment

If MOST is applied and especially in the context of multipurpose ECOS, artificial organ crosstalk should be considered by a multidisciplinary task force to avoid negative interactions and unwanted side effects. An integrated monitoring of patients, chemistry and machine parameters will offer the basis for "smart" biofeedback leading to correction in prescription and delivery of extracorporeal organ support (Ricci et al. 2017).

We strongly advocate the need for next generation ECOS machines to achieve harmonisation of components, techniques and operations of multiple extracorporeal therapies. We suggest the possibility to perform simultaneous multiple functions and techniques optimising artificial organ crosstalk while avoiding unwanted side effects or operational drawbacks due to poor integration of prescription and delivery parameters. Further studies are needed to establish the ideal timing of interventions, to find out whether early implementation impacts organ recovery and optimises resource utilisation, and to identify the patient groups that can be expected to benefit from long-term organ support. ■

Conflict of interest

Claudio Ronco declares he has no conflict of interest. Zaccaria Ricci declares he has no conflict of interest. Faeq Husain-Syed declares he has no conflict of interest.

Abbreviations

AHD albumin dialysis
AKI acute kidney injury
CKD chronic kidney disease
CPFA coupled plasma filtration adsorption
$ECCO_2R$ extracorporeal carbon dioxide removal
ECMO extracorporeal membrane oxygenation
ECOS extracorporeal organ support
HCO high-cut-off membrane
HP haemoperfusion
HRS hepatorenal syndrome
HVHF high volume haemofiltration
MODS/MOFS Multiple Organ Dysfunction/Failure Syndrome
MOST multiple organ support therapy
MV mechanical ventilation
PE plasma exchange
PF plasma filtration
PFAD plasma filtration adsorption dialysis
PP plasmapheresis
RRT renal replacement therapy
VAD ventricular assist device

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

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Chronic respiratory dialysis

Extracorporeal carbon dioxide removal is emerging as a potential strategy to manage acute hypercapnic respiratory failure. There may be an opportunity to use similar techniques to manage chronic hypercapnic respiratory failure, in what may be termed ìchronic respiratory dialysisî, potentially altering the physiological and clinical effects of chronic hypercapnia associated with certain chronic lung diseases.

The use of extracorporeal gas exchange support for respiratory failure has grown rapidly and in parallel with improvements in extracorporeal technology that have led to more efficient gas exchange with potentially more favourable risk profiles (Thiagarajan et al. 2017). This growth has predominantly come from the increased use of extracorporeal membrane oxygenation (ECMO) for the most severe forms of the acute respiratory distress syndrome (ARDS) (Karagiannidis et al. 2016). However, there is an evolving interest in the use of extracorporeal carbon dioxide removal ($ECCO_2R$) for both acute and chronic respiratory failure (Deniau et al. 2016; Morelli et al. 2017), with a current focus on its potential to facilitate the minimisation or avoidance of invasive mechanical ventilation and its associated consequences (Abrams and Brodie 2013). As the technology continues to evolve, the question arises as to whether $ECCO_2R$ could play a role in the management of chronic hypercapnic respiratory failure by decreasing the respiratory load in patients with advanced lung disease.

Differences between ECMO and $ECCO_2R$

Although technically consisting of the same circuit components as ECMO (e.g. cannulae, tubing, gas exchange membrane, and most frequently incorporating a centrifugal pump), the difference between ECMO and $ECCO_2R$ is that the intention of $ECCO_2R$ is specifically carbon dioxide removal without emphasis on oxygenation, whereas ECMO is intended to provide both carbon dioxide removal and significant oxygenation—a distinction that has important clinical implications. Oxygenation is, in large part, dependent on the amount of extracorporeal blood flow in order to saturate a sufficient amount of haemoglobin. This typically necessitates the use of large cannulae to achieve adequate blood flow to meet the needs of patients with severe hypoxaemia (Schmidt et al. 2013). In contrast, carbon dioxide removal is much more efficient than oxygenation, allowing for the use of lower blood flow rates than in ECMO, potentially even within the range of what may be used for continuous venovenous haemodialysis (CVVH), though without significant contribution to oxygenation. With less demand for blood flow, $ECCO_2R$ can be achieved with smaller cannulae, comparable to dialysis catheters, which may have an improved risk-benefit profile compared to ECMO (Morelli et al. 2017). Additional modalities that are being explored to further optimise the efficiency of $ECCO_2R$, by maximising the gradient of carbon dioxide across the membrane, include the use of electrodialysis, blood acidification and carbonic anhydrase (Arazawa et al. 2012; Zanella et al. 2015; 2014).

$ECCO_2R$ devices

The derivation of $ECCO_2R$ devices has come from several directions—downsizing of circuits originally intended for ECMO in order to accommodate lower blood flow rates (e.g. Novalung, Xenios AG, Heilbronn, Germany); modifications to circuits intended for CVVH (e.g. PrismaLung, Baxter, Illinois, USA); and devices designed specifically for the intention of providing $ECCO_2R$ (e.g. Hemolung RAS, ALung, Pennsylvania, USA). Conceptually similar, each of these devices may have circuit-specific advantages and risks, with no single device as yet proving to be superior for carbon dioxide removal over another. Several of these devices are being used as part of prospective, randomised controlled trials of $ECCO_2R$ for various aetiologies of acute respiratory failure (Fanelli et al. 2016; McNamee et al. 2017).

> "no consensus on what constitutes success of chronic respiratory dialysis"

Potential uses of $ECCO_2R$

In theory, $ECCO_2R$ can be used for any clinical scenario in which the goal is extracorporeal management of ventilation, and when oxygenation is supportable by other means. An area of active investigation is $ECCO_2R$ for ARDS in order to facilitate reductions in tidal volumes, plateau airway pressures, and respiratory rates to minimise the extent of ventilator-associated lung injury (VALI) (Abrams and Brodie 2013; Bein et al. 2013; Fanelli et al. 2016; Grasso et al. 2014; Terragni et al. 2009). Beyond ARDS, and perhaps the more obvious target of carbon dioxide removal is the potential role of $ECCO_2R$ in acute hypercapnic respiratory failure, such as may be encountered in acute exacerbations of chronic

Darryl Abrams
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University College of Physicians and Surgeons/ NewYork-Presbyterian Hospital
New York, USA

da2256@cumc.columbia.edu

Antonio Pesenti
Professor of Anesthesia and Critical Care
Department of Medico-Surgical Pathophysiology and Transplantation, University of Milan, and Fondazione C Granda Ospedale Maggiore Policlinico Milan, Italy

antonio.pesenti@unimi.it

Daniel Brodie
Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University College of Physicians and Surgeons/ NewYork-Presbyterian Hospital
New York, USA

hdb5f@cumc.columbia.edu

*corresponding author

obstructive pulmonary disease (COPD), cystic fibrosis, and severe status asthmaticus, among others. $ECCO_2R$-facilitated correction of respiratory acidosis has been shown to be feasible in patients with acute hypercapnic respiratory failure in the setting of COPD exacerbations that has either not responded to noninvasive ventilation (NIV), or has persisted despite invasive mechanical ventilation (Abrams et al. 2013; Del Sorbo et al. 2014; Kluge et al. 2012). $ECCO_2R$, through correction of the respiratory acidosis, may reduce the work of breathing (which, in turn, reduces the production of carbon dioxide by the respiratory muscles, decreasing the overall carbon dioxide load to be excreted) (Cardenas et al. 2009; Diehl et al. 2016), dynamic hyperinflation, and potentially the need for ongoing mechanical ventilatory support, in turn facilitating early mobilisation and rehabilitation and avoiding the complications of ventilator-associated pneumonia and worsening hyperinflation (Abrams et al. 2013). Similarly, $ECCO_2R$ has been used for acute hypercapnic respiratory failure in the setting of advanced chronic lung disease as a bridge to lung transplantation, often with the ability to avoid invasive mechanical ventilation prior to transplantation (Biscotti et al. 2017; Fuehner et al. 2012).

$ECCO_2R$ may be capable of correcting hypercapnic respiratory failure in the acute settings, but what about in the chronic setting as a means of consistently resetting carbon dioxide levels in patients with decreased ventilatory capacity from chronic lung disease? In this context, carbon dioxide removal could function as a form of chronic respiratory dialysis (Ranieri et al. 2017).

Carbon dioxide is stored in several forms within the body, the vast majority of which is as bone carbonate (very slowly exchanged) and bone bicarbonate (slowly exchanged) (Cherniack and Longobardo 1970). The remaining carbon dioxide is stored as blood bicarbonate, dissolved gas in plasma, carbamino compounds within erythrocytes, and free gas within alveoli, all of which is more readily exchanged. If an $ECCO_2R$ -like device could remove carbon dioxide at a rate and frequency that would allow for meaningful reductions in carbon dioxide stores that are not typically accessed, it may be theoretically feasible to recalibrate the baseline plasma carbon dioxide levels in patients with chronic hypercapnic respiratory failure. By decreasing the ventilatory requirements in patients with already limited ventilatory capacity, such a device might sufficiently reduce the work of breathing, the respiratory load and the amount of carbon dioxide produced, as well as facilitate improvement in the hyperinflation and gas trapping that increases dead space and puts respiratory muscles at a mechanical disadvantage (McKenzie et al. 2009; Tobin et al. 2009).

While theoretically this has the potential to be a therapeutic option, there are many aspects of chronic respiratory dialysis that require further investigation prior to any consideration of clinical application. Most importantly, there needs to be a better understanding of the kinetics of carbon dioxide exchange, particularly in regards to the rate of exchange between blood and bone or other stores of carbon dioxide (Cherniack and Longobardo 1970). This relationship will help inform the frequency and intensity of $ECCO_2R$ that would need to be applied on a chronic basis to have a meaningful effect on carbon dioxide levels. Mathematical modelling and physiological studies would be helpful in providing this information.

Secondly, in whom should chronic respiratory dialysis be considered? Patients with COPD with chronic hypercapnic respiratory failure have shown variable responses to the chronic use of NIV on blood carbon dioxide levels and exacerbation rates (Elliott et al. 1991; Meecham Jones et al. 1995; Murphy et al. 2017; Ramsay and Hart 2013; Struik et al. 2014). The discrepancy in findings from two randomised controlled trials of NIV for the management of hypercapnia that persisted after acute exacerbations of COPD highlights an important point regarding the potential use of carbon dioxide removal for the management of chronic hypercapnia (Murphy et al. 2017; Struik et al. 2014). NIV may be effective in maintaining long-term control of hypercapnia in some patients and is clearly a less invasive approach than carbon dioxide removal (Ramsay and Hart 2013). However, there are patients within this population who are non-responders to long-term NIV management, particularly as it relates to control of hypercapnia, and perhaps would be suitable for chronic respiratory dialysis as an alternative. The data for efficacy of NIV for the management of hypercapnia in cystic fibrosis and other forms of bronchiectasis are limited to small trials with inconsistent results (Moran et al. 2017). Select patients within these populations who are non-responsive to or intolerant of NIV may likewise be considered potential candidates for chronic respiratory dialysis.

Identifying the appropriate subset of patients that should be studied will require further analysis of existing data and prospective trials that are ideally enriched with patients most likely to respond to the use of chronic carbon dioxide removal based on physiologic and other predictive factors. This type of modelling has been proposed in the acute setting (Goligher et al. 2017; Lindberg et al. 2017). There are also practical applications that should be considered, including how one would actually physically initiate carbon dioxide removal and whether this might influence the target population for further study. Patients with chronic hypercapnic respiratory failure and end-stage renal disease who receive haemodialysis through tunnelled catheters or arteriovenous fistulae or grafts would have pre-existing access that might be suitable for the application of carbon dioxide removal. To that end, future iterations of carbon dioxide removal technology might be combined with renal dialysis machines, facilitating the performance of both processes simultaneously (Forster et al. 2013; Husain-Syed et al. 2016; Quintard et al. 2014; Romagnoli et al. 2016). However, the convenience of studying such a patient population may be offset by the coexisting burden of comorbidities that may negatively impact any long-term benefit gained from chronic respiratory dialysis. Instead, if patients were to require dedicated access for carbon dioxide removal, one must consider what form that

would take—tunnelled catheter, fistula, graft—and whether that access would be appropriate to sustain the low blood flow rates typically used for $ECCO_2R$.

Conceptually, the idea of intermittent $ECCO_2R$ for chronic hypercapnic respiratory failure does not differ to any great degree from a hypothetical destination device for the support of severe, end-stage respiratory failure from other aetiologies, a so-called artificial lung, which could likewise be referred to as 'chronic respiratory dialysis'. The main practical differences would be the intermittent versus continuous use of the device, and whether carbon dioxide removal alone, or both carbon dioxide removal and oxygenation are needed, which would have significant implications for the amount of blood flow needed and the type and source of gas supplied.

When considering chronic respiratory dialysis, special attention will need to be paid to its effect on the physiology of gas exchange. A carbon dioxide removal device that removes a considerable amount of carbon dioxide while contributing a negligible amount to oxygenation may have unanticipated consequences for oxygenation. Imagine that fifty percent of the total body carbon dioxide production is removed by the device, with unchanged oxygen transfer by the patient's native lungs. The respiratory exchange ratio of the native lungs would then be reduced by half, to approximately 0.4 (from a normal value of 0.8). According to the alveolar gas equation, the partial pressure of oxygen in the alveolus would reach unacceptably low levels, and an enrichment of the inspired fraction of oxygen would become necessary.

Economic considerations

In addition to the clinical implications, one must consider the potential economic impact of such a strategy on, potentially, a very large patient population for a long period of time, much in the way haemodialysis has impacted patients with advanced renal failure (Li et al. 2017). Aside from the cost of the technology itself, the potential of increasing the life expectancy of patients known to have multiple comorbidities (e.g. cardiovascular disease) may substantially increase overall healthcare costs (Wacker et al. 2017).

What constitutes success?

Lastly, there is no consensus on what constitutes success of chronic respiratory dialysis. Normalisation of the carbon dioxide in a chronic respiratory acidosis may be achievable as a physiological endpoint, but it must also demonstrate improvement in clinically meaningful outcomes for it to have any role in clinical practice. Quality of life, exercise capacity, rate of exacerbations, and mortality would all be appropriate endpoints for future studies, accompanied by the applicable cost-benefit analyses.

Conclusion

In conclusion, advances in extracorporeal gas exchange have created an opportunity to intervene upon both acute and chronic hypercapnic respiratory failure. A better understanding of the physiology behind carbon dioxide metabolism and how that might impact the application and effectiveness of chronic respiratory dialysis is needed in order to understand which patients might benefit from this potential therapeutic strategy. ■

Conflict of interest

Daniel Brodie is currently the co-chair of the Trial Steering Committee for the VENT-AVOID trial sponsored by ALung Technologies. He was previously on the medical advisory board of ALung Technologies and Kadence (Johnson & Johnson). All compensation for these activities is paid to Columbia University. Darryl Abrams and Antonio Pesenti declare that they have no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome

COPD chronic obstructive pulmonary disease

CVVH continuous venovenous dialysis

$ECCO_2R$ extracorporeal carbon dioxide removal

ECMO extracorporeal membrane oxygenation

NIV noninvasive ventilation

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Understanding LVAD & artificial hearts

Regarding the growing number of patients with long-term mechanical assist devices, intensivists need to understand the physiology of the devices, their functioning, potential complications and their management.

Nadia Aissaoui[1,2]*

Nadia.aissaoui13@gmail.com

Aymeric Lancelot[1]

Romain Pirracchio[3]

Long-term mechanical circulatory support (MCS) is being used increasingly for patients at risk of dying from heart failure and cardiogenic shock (Ponikowski et al. 2016; Gustafsson and Rogers 2017). As a result, intensivists who do not have training in managing advanced heart failure patients are increasingly likely to encounter patients requiring MCS at various points in the trajectory of their disease, especially during subsequent admissions for complications (Pratt et al. 2014; DeVore et al. 2014). A basic understanding of ventricular assist device (VAD) physiology is essential for the safe and effective care of these patients. This review highlights the physiology of patients with MCS and management of common complications relevant to the critical care physicians.

Indications of long-term MCS

MCS systems can be used to unload the failing ventricle and maintain sufficient end-organ perfusion. While heart transplantation (HT) is a highly effective therapy for advanced refractory heart failure (HF), it is limited to <10% of candidates, due to a severe shortage of donor organs and a variety of contraindications (Ponikowski et al. 2016; Aissaoui et al. 2018). This paucity of effective therapy promoted the development of VAD, which may be used as a) a bridge to HT or b) a long-term alternative to HT, also known as destination therapy.

Depending on which ventricle is assisted, three categories of long-term MCS are available: left VAD, biventricular assist device, and total artificial heart (TAH) (Ponikowski et al. 2016; Mehra et al. 2017).

Improvements in technology, especially the advent of smaller, durable continuous flow pumps, have led to the use of LVADs in a much broader population of patients in the last 10 years (Gustafsson and Rogers 2017). It is estimated that 2000 pumps are implanted annually in Europe. Compared with LVADs, TAH is implanted in a much smaller subset of patients (Cook et al. 2015; Torregrossa et al. 2014). Data from the most recent analysis from the LVAD registry show a one-year survival rate of 80% (Gustafsson and Rogers 2017). Concerning TAH patients, the most recent multicentre studies reported a one-year survival rate between 56% to 76% (Cook et al. 2015; Torregrossa et al. 2014).

Device physiology: what should intensivists know?

Management of these patients requires an understanding of the principles, indications and limitations of this unique technology.

LVAD. LVAD are intracorporeal rotary pumps that unload the LV continuously. A percutaneous driveline connects the pump to an external controller and a power source (Gustafsson and Rogers 2017). The three currently approved LVADs are the HeartWare HVAD (HeartWare International, Inc. Framingham, MA), the HeartMate II (Thoratec Corporation, Pleasanton, CA) and the newest HeartMate 3™ (Thoratec Corporation, Pleasanton, CA) (Mehra et al. 2017) (**Figure 1**). Pump parameters are key and include the following (**Figure 1**) (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014; Estep et al. 2015).

Pump speed (revolutions per minute, RPM) is the only variable programmed by the operator. For each patient, it is adjusted after implantation by the heart failure physician [between 8000 and 10000 rpm for HeartMate II, 2400-3200 rpm for HeartWare and 4000-6000 rpm for HeartMate 3].

Pump flow is the blood flow displayed on the LVAD monitor and calculated based on measured pump power and set pump speed. The device flow is directly proportional to the pump speed and inversely related to the LV intracavitary pressure, i.e. the difference of pressure in the inflow and outflow cannulas (**Figure 2**). Any change in pump function or in patient condition may lead to significant changes in pump flow.

Pump power is a direct measurement of watts required by the device to pump blood at the set RPM. It may be affected by LVAD obstruction.

The Pulsatility index corresponds to the magnitude of flow pulse through the pump. It fluctuates with changes in volume status and with heart contractility (Heartmate II and 3).

Total artificial heart. For patients with severe biventricular failure and/or valvular mechanical prosthesis, a TAH may be an option (Cook et al. 2015; Torregrossa et al. 2014). TAHs replace all functions of the native heart. The most used TAH is the CardioWest TAH consisting of two polyurethane ventricles (**Figure 3**). The newest CARMAT TAH, an implantable electro-hydraulically actuated pulsatile biventricular pump will probably replace the CardioWest TAH in the future (Latrémouille et al. 2018). The CardioWest device is typically set to partially fill and runs at a fixed percentage of systole and a fixed beat rate of 120 to130 bpm with a stroke volume of 50–60 mL (Cook et al. 2015; Torregrossa et al. 2014). The clinician can modify several parameters to optimise cardiac output: beat rate, drive pressure, percentage of time in systole, and vacuum pressure. Depending on exercise or volume status, the cardiac output may automatically increase in response to an increase in venous return and preload such as in a normal heart.

Which medication and specific care are required in VAD patients?

Anticoagulation and antiplatelet therapy. Anticoagulation protocols vary by institution, device, and individual patient. Patients are typically receiving therapy with aspirin (81–325

Jérôme Jouan[4], Maxence Le-guyader[1], Jean-Luc Diehl[1], Etienne Puymirat[5], Clotilde Bailleul[1], Bernard Cholley[3], Michiel Morshuis[6]

[1.] Assistance Publique-HÙpitaux de Paris (AP-HP); HÙpital EuropÈen Georges Pompidou (HEGP), Department of Critical Care Unit, Paris, France; UniversitÈ Paris-Descartes, Paris, France
[2.] Paris-Cardiovascular-Research-Center, INSERM U970, Paris, France
[3.] Heart and Diabetes Centre NRW, Ruhr-University of Bochum, Department of Thoracic & Cardiovascular Surgery, Bad Oeynhausen, Germany
[4.] Assistance Publique-HÙpitaux de Paris (AP-HP); HÙpital EuropÈen Georges Pompidou (HEGP), Department of Cardiac Surgery, Paris, France; UniversitÈ Paris-Descartes, Paris, France
[5.] Assistance Publique-HÙpitaux de Paris (AP-HP); HÙpital EuropÈen Georges Pompidou (HEGP), Department of Cardiology, Paris, France; UniversitÈ Paris-Descartes, Paris, France
[6.] Assistance Publique-HÙpitaux de Paris (AP-HP); HÙpital EuropÈen Georges Pompidou (HEGP), Department of AnesthÈsie-rÈanimation, Paris, France; UniversitÈ Paris-Descartes, Paris, France

*corresponding author

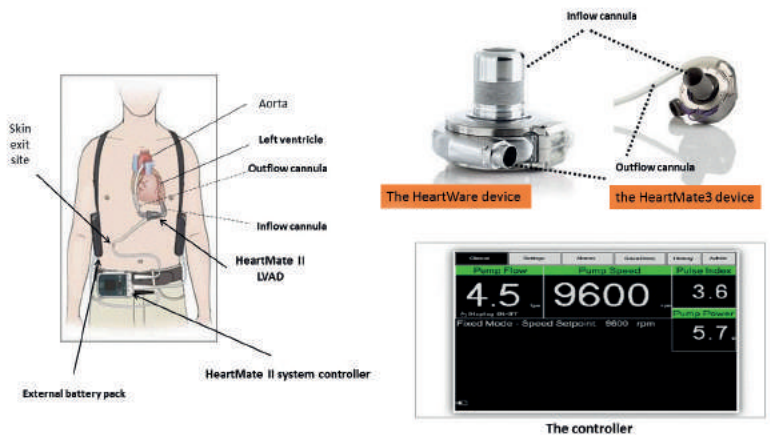

Figure 1. Principles of left ventricule assist device

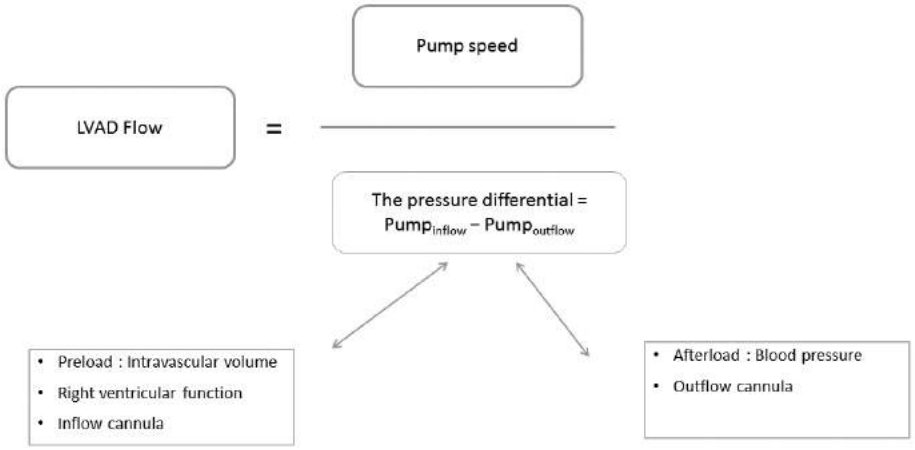

Figure 2. Determinants of pump flow

mg) and warfarin (goal INR 2.0–3.0) (Gustafsson and Rogers 2017; Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014; Cook et al. 2015; Torregrossa et al. 2014; Mehra et al. 2017). Management of MCS patients requires assessment of the risks of thrombosis and haemorrhage (Suarez et al. 2011).

Medications of advanced HF. Despite the lack of evidence and in order to favour weaning, the guidelines used for patients under MCS are those used for heart failure patients (Gustaffson and Rogers 2017). Specifically, and according to the most recent International Society of Heart and Lung Transplant (ISHLT) guidelines, mean blood pressure (BP) should be lower or equal to 80 mm Hg with a typical goal range between 70 and 80 mmHg to prevent stroke and LVAD dysfunction due to increased afterload (Estep et al. 2017).

Driveline. The most important factor in preventing the morbidity of infections is anchoring the device to help stabilise the driveline, thus minimising trauma and tension at the exit site (Gustafsson and Rogers 2017; Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014). The patient follows a sterile dressing care regimen in accordance with protocol and has to monitor the driveline exit site for redness, drainage, tenderness and open areas at the site.

Why do patients with LVAD come into the ICU?

The most frequent complications occurring in MCS patients are bleeding, driveline infections, thrombosis, device malfunction, right ventricular (RV) failure and arrhythmias (Gustafsson and Rogers 2017; Cleveland et al. 2011; Feldman et al. 2013). Patients with MCS can also be admitted to the ICU for non-specific aetiologies (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014).

The implanting hospital and VAD coordinator should be contacted for each MCS patient requiring admission into the ICU (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014; Mehra et al. 2017). Some patients may be managed by non-LVAD specialists after advice and agreement of the implanting team whereas all TAH should be transferred to the implanting hospital.

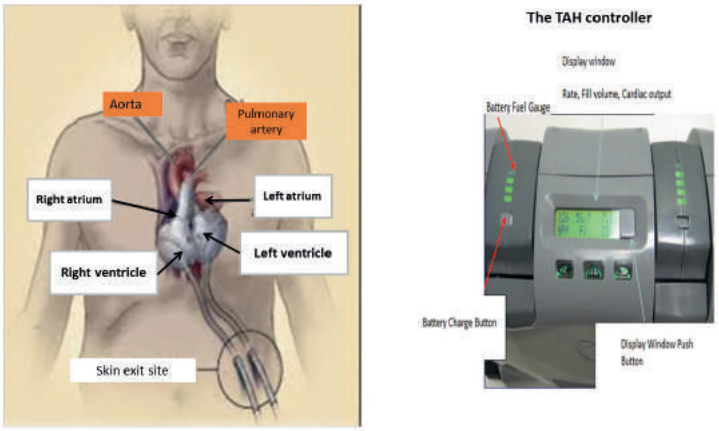

Figure 3. Principles of Syncardia Total Artificial Heart

Frequent complications in MCS patients

Bleeding is the most frequent adverse event in MCS due to combination anticoagulation and acquired von Willebrand disease due to the sheer stresses in the pump (Suarez et al. 2011). Bleeding events (after one month from VAD implantation) are epistaxis, gastrointestinal bleeding, intracranial haemorrhage and mediastinal and thoracic bleeding.

Infection is the second most common cause of death after cardiac failure in MCS patients (Estep et al. 2015; Feldman et al. 2013). The driveline exit sites need special attention. An infection can develop and ascend up to the device. LVAD-specific infections are located on the driveline or pump pocket (Kusne et al. 2017). They need aggressive treatment by including blood culture: blood cultures, antibiotics, surgical debridement, and even HT (Kusne et al. 2017).

Major thrombotic events in LVAD patients include pump thrombosis and arterial thromboembolism.

One of the common causes of a low cardiac output state is device thrombosis, which occurs in approximately 8% (per year) of implanted, continuous-flow LVAD (Aissaoui et al. 2012). Signs of pump thrombosis include haemolysis, thromboembolism events, heart failure, and, ultimately, cardiogenic shock with elevated power uptake and high calculated flows (reading on the LVAD controller). Such patients will need increased anticoagulant medications, thrombolytic therapy, a device exchange or urgent HT (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014; Feldman et al. 2013; Aissaoui et al. 2012). Device thrombosis can develop even when patients are fully anticoagulated and taking antiplatelet therapy, because the LVAD causes a chronic hypercoagulable state (Aissaoui et al. 2012).

The major complications of TAH implantation include strokes, infection, bleeding, thrombosis, renal failure and chronic anaemia (Cook et al. 2015; Feldman et al. 2013).

Cardiac arrest. Consequences of cardiac arrest on pump function highly depend on cardiac rest function. While some patients will collapse immediately, others may even be able to exercise. The impact of ventricular arrhythmia is also variable, sometimes creating some kind of Fontan circulation, with a sufficient output flow. In general, LVAD patients in cardiac arrest who are collapsing should be managed according to the Advanced Cardiac Life Support (ACLS) recommendations, with some precautions (Hazinski et al. 2015; Nolan et al 2015).

> "infection is the second most common cause of death after cardiac failure in MCS patients"

The major risk factor to chest compressions during cardiopulmonary resuscitation is dislodgement of the device or its outflow cannula, located directly beneath the sternum (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014). A potential alternative to chest compression is abdominal compression 1 to 2 inches left of midline, as previously described although still not currently recommended (Pratt et al. 2014; Sen et al. 2016).

Patients with device stoppage can present in severe cardiogenic shock or full arrest and should be managed appropriately while searching for the cause of malfunction. In these cases, the VAD coordinator should be contacted immediately and all of the VAD equipment should be assessed to verify that critical connections are intact. The driveline and power supply should be checked and reconnected if disconnected (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014). Alarms should be assessed. If there is a VAD hum, it should be assessed with auscultation. Doppler ultrasonography should be used to evaluate the patient's BP and echocardiography to assess some haemodynamic parameters and look for VAD complications.

Once restarted, a major concern is thromboembolism from the device. Device exchange can be performed emergently if necessary and feasible.

Electrical activity without cardiac contractility should prompt a search for underlying causes, such as tension pneumothorax and electrolyte derangements.

Noncardiac surgery. Noncardiac surgery presents an increased risk of morbidity due to bleeding (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014). However, it can be performed if a VAD coordinator or nurse familiar with the management of the device accompanies patients in the operating room to manage the console, monitor LVAD flow and address any alarms. If emergency surgery at a centre without VAD support is necessary, care providers should call the manufacturer or nearest hospital with a VAD programme to obtain advice and recommendations on management of the device. Intra-abdominal procedures must proceed with extreme caution to avoid encountering the subcutaneously tunnelled driveline. Ultrasound can be used to mark the driveline's location. No protocols exist for managing anticoagulation in the perioperative period, and a variety of approaches have been used.

Suction events. A suction event occurs when there is reduced filling of the pump (reduced preload), which increases negative pressure within the LV. During this event, part of the LV wall is *sucked over* and covers the pump's inlet cannula, generating an alarm and a decrease of speed to release the suction. Suction events are caused by low volume, RV failure or tamponade. Suction events can lead to low LVAD flows and can trigger ventricular arrhythmias. The management includes decreasing the RPM rate and administering fluid.

Specific monitoring

Blood pressure. Contrary to TAH patients, it can be difficult to record BP using traditional measurements in LVAD patients with a reduced pulse pressure (Estep et al. 2015). A Doppler ultrasound probe that detects flow at any point during the cardiac cycle and measures an opening pressure may be useful. In cases of shock, an arterial catheter should be inserted for continuous mean arterial pressure (MAP) monitoring and is best placed via ultrasonographic guidance (continuous flow makes blind placement difficult) (Pratt et al. 2014; Sen et al. 2016; DeVore et al. 2014; Estep et al. 2015).

Echocardiography. Echocardiography is fundamental in the management of LVAD patients but should be interpreted with knowledge of the patient's clinical status (Stainback et al. 2015).

Table 1. Management of the main alarm

Alarms	Signification	Action
Steady tone and no symbol	No power to the device	Check all connections immediately
Red alarm	1. Disconnection of the driveline from the controller	Check the connections
	2. Low flow	Clinical assessment and echocardiography: • hypovolaemia • bleeding • tamponade • RV failure • hypertension • or cannula obstruction
Yellow system	Low cell voltage	Check the power source and the power leads
Green advisory alarm	1. Power cable disconnection 2. The power symbol and battery power bars flash	Check the power source and the power leads

It is useful to assess haemodynamic parameters:

- LV size and function
- Position of the ventricular septum (flat and neutral)
- Competency of the aortic valve (it should be competent and open intermittently, every second or third beat)
- RV size and function
- Inferior vena cava and collapsibility
- Signs of pericardial effusion or tamponade
- Inflow cannula (if visualised) aligned with the mitral valve; and
- Outflow cannula (if visualised).

Bedside echocardiography can also detect and/or diagnose LVAD complications. It is useful in TAH patients.

Advisory alarms. **Table 1** reports the main alarms to look out for and to manage.

If there is a steady tone and no symbol, there is no power to the device. All connections should be checked immediately (the system driver connections to the device and the system driver and power connections to the power source), because patients may be at risk of cardiopulmonary arrest.

The red hazard alarm can indicate disconnection of driveline from the controller, low flow or incorrect operation, and so the connections need to be checked. It may also suggest hypovolaemia, bleeding, tamponade, RV failure, hypertension, or cannula obstruction. In these cases, both the patient and the device should be assessed emergently.

The yellow system driver signals low cell voltage. When this occurs, the cell battery should be replaced and a system controller self-test performed. The green advisory alarm signals a power cable disconnection; the power symbol and battery power bars flash. Cable connections to the power source should be checked and power leads should be assessed for damage and replaced if necessary. ■

Conflict of interest

Nadia Aissaoui declares receipt of Medtronic grant for congress participation. All other authors declare that they have no conflict of interest.

Abbreviations

HF heart failure
HT heart transplanatation
LVAD left ventricular assist device
MCS mechanical circulatory support
TAH total artificial heart
VAD ventricular assist device

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Optimising patient–ventilator synchronisation

Report on the Hamilton Medical symposium, LIVES 2017, Vienna, Austria, 26 September 2017

Dr. Lluís Blanch, Dr. Jean-Michel Arnal and Prof. Francesco Mojoli discuss why patient-ventilator synchrony is important, how to detect asynchronies, and technical solutions for optimising synchronisation.

Definition and clinical effects

Patient-ventilator asynchrony occurs when there is a mismatch between the patient's inspiratory time and the mechanical breath (phase asynchrony) or when the flow provided by the ventilator is inadequate (flow asynchrony). It is a common occurrence, with up to one quarter of mechanically ventilated patients showing a high incidence of phase asynchrony (Thille et al. 2006). Suboptimal interaction between patient and ventilator can have wide-ranging physical and psychological effects, including dyspnoea and air hunger, discomfort, anxiety, and lung injury. These effects on the patient may often go undetected by healthcare staff, with nurses and physicians underestimating the feeling of breathlessness and impaired respiratory function as reported by the patients during a spontaneous breathing trial (Haugdahl et al. 2015).

Asynchronies may have a significant effect on patient outcomes, including a longer duration of mechanical ventilation and a higher rate of tracheostomy (Thille et al. 2006). De Wit and colleagues (2009) found a higher ineffective triggering index to be associated with a longer duration of mechanical ventilation as well as a longer hospital stay, while Blanch and colleagues (2015) found that an asynchrony index of greater than 10% was associated with increased ICU and hospital mortality. Their study analysed asynchronies, including ineffective inspiratory efforts, premature cycling and delayed cycling, in 50 patients monitored for a total of over 8 million breaths, which represented a median of almost 83% of the total time each patient received mechanical ventilation. The data showed that asynchronies were not only always present (**Fig. 1**), but also unpredictable. The asynchrony index for four patients rose and fell with no recognisable pattern over periods of at least 100 hours (**Fig. 2**). Avoiding asynchronies is therefore a difficult task, as it is not possible to predict when they will occur and when the settings might need to be changed accordingly.

The role of assistance levels and sedation

The level of pressure support is an important factor that may affect certain patient-ventilator asynchronies. A higher level of pressure support has been associated with ineffective inspiratory efforts (Thille et al. 2006) and an increase in the level of assistance appears to intensify the problem of cycling delays significantly during pressure-support ventilation (Spahija et al. 2010). Brochard and colleagues (2007) also found that ineffective inspiratory efforts during pressure-support ventilation may increase due to a high level of pressure support, as well as auto PEEP, inadequate triggering and delayed cycling. However, over-assistance is also associated with less dyspnoea and thus greater patient comfort. Under-assistance, conversely, is associated with more dyspnoea but fewer ineffective inspiratory efforts (Schmidt et al. 2013).

Several studies have examined the role of sedation with respect to patient-ventilator synchrony. Deeper sedation is associated with a greater incidence of ineffective inspiratory efforts (de Wit et al. 2009; Vaschetto et al. 2014), while the absence of sedation has been linked with improved outcomes in terms of the number of days without mechanical ventilation and the length of ICU and hospital stay (Strom et al. 2010). De Haro and colleagues are currently investigating the relationship between the asynchrony index and sedation, opioids and neuromuscular blockers.

Recognising asynchronies

The easiest way to recognise asynchronies at the bedside is to observe the patient and see if their inspiratory effort matches the mechanical breath. However, clinical observation is limited to severe asynchronies with a long enough delay between the patient's effort and the mechanical breath (e.g., > 300 ms). In obese patients, it may be necessary to touch the respiratory muscle to feel when the effort starts. The clinician can certainly ask the patient simple questions about their breathing, especially if they are on noninvasive ventilation (NIV), however considering the unpredictability of asynchronies it is not feasible to monitor them constantly in this way.

Analysis of waveforms

More precise assessment of synchronisation at the bedside relies on the interpretation of ventilator waveforms. Pressure and flow waveforms display the interactions between the mechanical breath and the respiratory mechanics and patient's effort, and studies have shown them to be an extremely useful tool for identifying asynchronies (Georgopolous et al. 2006; Mojoli et al. 2016). On the waveforms, the beginning of the patient's inspiration can easily be detected as a sudden negative deflection in pressure tracing, and/or a sudden positive deflection of flow. However, it may be somewhat more difficult to see when the patient effort finishes and how much effort the patient is making.

The question of whether the ventilator is switching from inspiration to expiration at the right time can usually be answered by looking at the waveforms, in particular the flow (Mojoli et al. 2016). For example, when the ventilator is late in opening the expiratory valve, a sudden change from a fast to a slow decrease in the inspiratory flow marks the end of the patient's inspiration and the beginning of a secondary phase of passive inflation.

The waveforms contain all the necessary information, however interpreting them is not always that simple. In a study carried out by Ramirez et al. (2017), only a very small number of healthcare professionals were able to recognise three simple asynchronies. Regardless of whether nurse or physician, or the years of experience in the ICU, it was shown that the only factor influencing the ability to interpret waveforms is training. Those staff members who had undergone relevant training were able to read the graphical representations correctly.

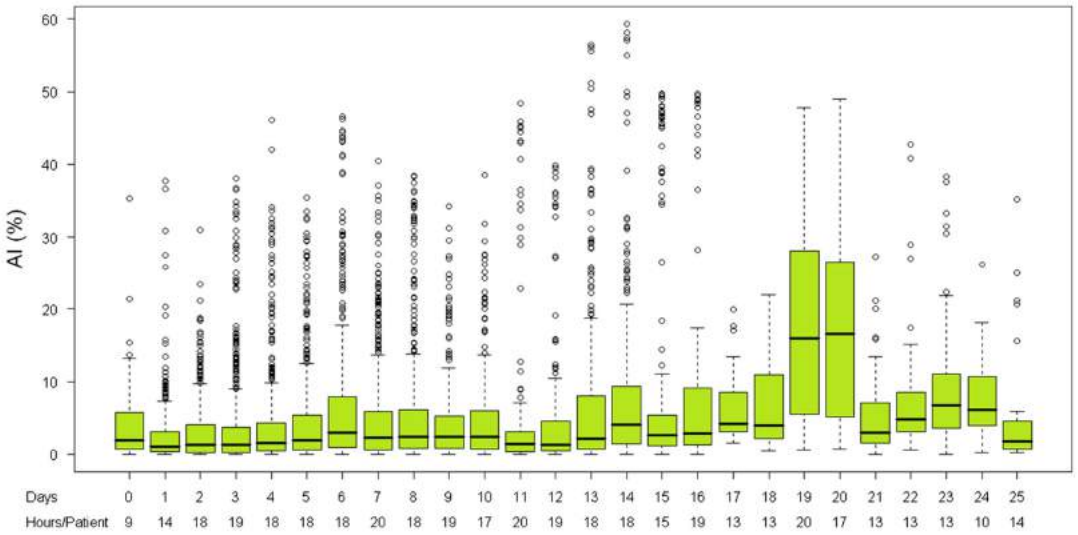


Figure 1. Asynchrony Index (AI) in 24-hour periods over 25 consecutive days of MV for all patients

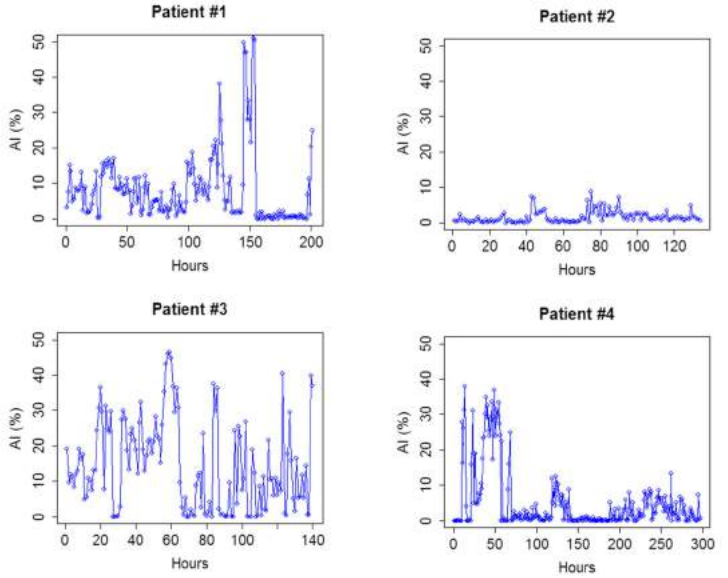


Figure 2. Trend of AI (%) in four patients

Oesophageal pressure measurement

The patient effort signal can be measured using oesophageal pressure, which is currently the gold standard. The start of the effort is easily identified by the negative swing in oesophageal pressure, and it is also possible to see how deep the effort is. The end of the effort occurs during the relaxation phase when the oesophageal pressure increases to baseline. If oesophageal pressure measurement is not available, we can also assess the inspiratory effort via an electromyography of the diaphragm using an oesophageal catheter or surface electrode. While this method may be more accurate than waveforms for certain asynchronies, it can be noisy and difficult for clinical use in practice and may thus be better suited for research purposes. Furthermore, waveform analysis remains the best method of recognising ineffective triggering.

Types of asynchronies

The table overleaf shows different types of asynchronies, how they can be recognised by patient observation and how they appear on the waveforms.

In some cases, multiple types of asynchronies may be interdependent. Inspiratory trigger delays, for example, usually cause late cycling - the breath starts later than it should and therefore also ends later. This gives rise to a vicious circle, whereby delayed cycling promotes dynamic hyperinflation and worsens intrinsic PEEP, inducing inspiratory trigger delay and leading to an increase in the number of ineffective inspiratory efforts and a greater workload for the respiratory muscle (Gentile et al. 2011).

Managing the most common asynchronies

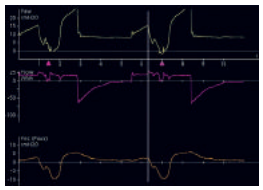
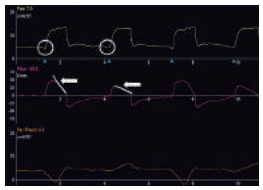
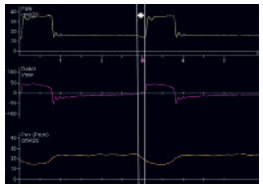
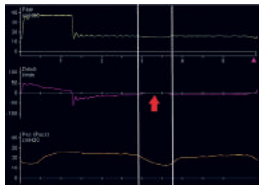
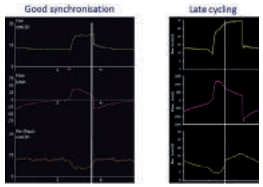
These cycling delays and ineffective inspiratory efforts are two of the most common forms of asynchrony. In patients undergoing prolonged pressure-support ventilation, cycling was found to be delayed in more than 50% of the patients' breaths (Mojoli et al. 2014). When at the bedside, clinicians can rectify the problem of cycling delays by adjusting the expiratory trigger sensitivity according to what they see on the ventilator screen. Alternatively, they can set the ventilator to open the expiratory valve as soon as a sudden change from fast to slow is detected in the decrease of the inspiratory flow. However, this requires the clinician to be at the bedside to identify the delay and change the settings.

Vaporidi and colleagues (2017) investigated clusters of ineffective inspiratory efforts (IEs) and their impact on patient outcomes. These clusters, defined as more than 30 ineffective inspiratory efforts during a 3-minute period, occurred in 38% of patients and were shown to be associated with a longer duration of mechanical ventilation and increased hospital mortality. Interestingly, the results of this particular study showed no correlation between patient outcomes and the IEs index in general, indicating that the clusters of ineffective inspiratory efforts may be of greater relevance. This conclusion demonstrates the importance of being able to monitor patients over an extended period of time to allow for the detection of such clusters that may occur at random.

What is needed to optimise synchronisation?

Improving patient-ventilator synchrony not only requires the clinicians to be trained in recognising the asynchronies, but also to be able to adjust

Table 1. Different asynchronies and how to identify them from the waveforms

	Clinical observation	Waveform characteristics
Reverse triggering		
	• Passive inflation that induces an inspiratory effort in a repetitive pattern • Occurs in heavily sedated patients • Difficult to see with clinical observation, easier to recognise from oesophageal pressure	• Distortion of the pressure and flow waveforms after the beginning of a ventilator-triggered breath
Phase asynchronies		
Auto-triggering		
	• Mechanical breath without an inspiratory effort • Mismatch between the respiratory rate (RR) on the ventilator and of the patient	• No decrease in pressure just before the mechanical breath • Maximum inspiratory flow is reduced because there is no patient effort • Inspiratory time constant is different for patient-triggered and auto-triggered breaths
Inspiratory trigger delay		
	• Delay between patient effort and mechanical breath • Evident from patient observation if the delay is long enough	• Delay between the start of the effort and the mechanical breath (increase in pressure) can be seen on the pressure curve and measured
Ineffective inspiratory effort		
	• Inspiratory effort which does not trigger a mechanical breath, usually associated with over-assistance • Evident from patient observation	• Indicated by a flow and pressure distortion to the baseline during expiration
Premature cycling		
	• Mechanical breath is shorter than the duration of the patient's effort	• Indicated by a short inspiration time • Peak expiratory flow is lower than for a normal breath • Distortion of expiratory flow can be seen at the start of expiration

the settings whenever asynchronies occur. Due to the unpredictable nature of asynchronies, the fixed trigger settings that were selected for a patient in the morning may no longer be suitable a few hours later. Optimising synchronisation would therefore require constant monitoring, which is not possible in practice. The solution would appear to lie in some form of continuous waveform reader integrated into the ventilator, which is able to replicate the capability of the clinician's eye and brain. Based on the waveforms, the trigger settings could then be adjusted automatically to prevent the occurrence of asynchronies.

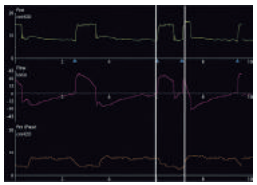
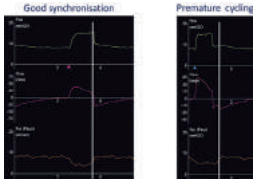
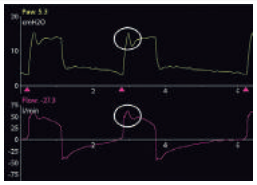
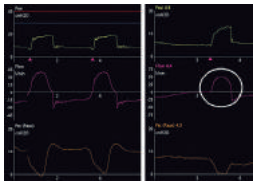
Automatic waveform-guided cycling-off and triggering

A new technology-based solution (IntelliSync+, Hamilton Medical AG) has therefore been developed to improve synchronisation, where both triggering and cycling-off are guided by automatic waveform analysis. As soon as a positive deflection of flow is detected, the ventilator opens the inspiratory valve and provides pressure support. While the highest sensitivity of conventional flow triggers is 0.5 l/min, this automatic analysis of real-time waveforms can detect an inspiratory effort even if the flow is still negative. This new technology continuously analyses waveform shapes to enable immediate detection of signals of patient effort or relaxation, and real-time initiation of inspiration and expiration. The clinician can decide whether to automate either the inspiratory trigger or cycling-off, or both.

Automatic waveform-guided optimisation vs. standard cycling-off

A pilot study compared the new technology for automatic waveform-guided optimisation with standard cycling-off at both the default expiratory trigger sensitivity (ETS) setting (25% of peak inspiratory flow) and a manually optimised setting guided by an analysis of waveforms (Mojoli et al. 2016). The comparison was made for two different levels of pressure support. Compared to the default ETS setting, the optimised ETS setting resulted in a reduction in cycling delays and ineffective efforts at the base level of pressure support. However, the investigators found that this same optimised ETS setting was no longer beneficial at the higher pressure-support level (base level + 50%). With the increase in pressure support, patient-ventilation interaction worsened and repeated

Table 1 (cont.) Different asynchronies and how to identify them from the waveforms

Double triggering		
	• Two mechanical breaths triggered by one single patient effort	• Two breaths can be seen on the pressure or flow waveforms
Late cycling		
	• Mechanical breath prolonged during patient expiration • Evident from patient observation	• Rise in pressure at the end of inspiration (patient is stopping the inspiratory effort) • Sudden change from a fast to a slow decrease in inspiratory flow • With strong inspiratory efforts, relaxation of the effort may cause a small pressure increase – this does not mean delayed cycling
Flow asynchronies		
Flow overshoot		
	• Flow provided by the ventilator is higher than the patient's demand	• Pressure overshoot at the beginning of inspiration
Flow starvation		
	• Flow provided by the ventilator is lower than the patient's demand	• Inspiratory-flow waveform has a round instead of triangular shape

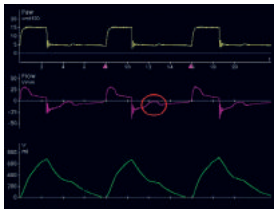


Figure 3a. Late cycling and ineffective efforts with manually set trigger settings (simulated patient data)

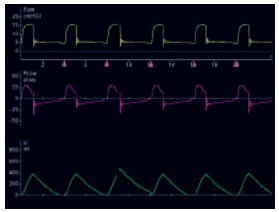


Figure 3b. Improved patient-ventilator interaction with IntelliSync+ activated for cycling-off (simulated patient data)

optimisation was required. This second optimisation led to a decrease in cycling and trigger delays, but did not affect the ineffective inspiratory efforts. Automatic optimisation of triggers using IntelliSync+ resulted in a significant decrease in cycling delays when compared to the manually optimised settings, with values of less than 100 ms at both pressure levels. The investigators found a similar reduction in ineffective efforts and trigger delays for manually and automatically optimised settings.

Changes to pressure support require new trigger settings

These results show that settings at one level of pressure support are no longer suitable at a higher level of support, and correspond with the findings of earlier studies that high pressure support significantly increases cycling delays and may lead to less inspiratory effort and therefore an inability to trigger. Each increase in pressure support requires an adjustment to trigger sensitivity to ensure patient-ventilator interaction does not worsen. Furthermore, even manual optimisation of fixed trigger settings may be insufficient, as this is based on an average of several breaths, whereas the automatic optimisation is performed on a breath-by-breath basis.

Conclusion

Automatic optimisation of trigger settings based on waveforms may therefore be a promising noninvasive tool for a new generation of pressure-support ventilation. The analysis of waveforms by the expert eye is a reliable way of detecting asynchronies, however the unpredictable nature of asynchronies would mean continuous monitoring is required. Preliminary evidence shows that automatic, waveform-guided optimisation performs just as well as, if not better than manual optimisation, and improves patient-ventilator interaction without the need for 24-hour surveillance. ■

References

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

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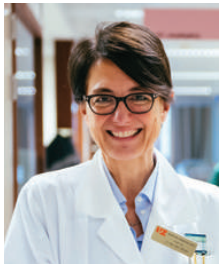
Chairperson of the Satellite Symposium: Greet Van den Berghe, MD, PhD

Nutritional Challenges in ICU patients

This symposium explored controversial aspects of the nutritional management of patients in the ICU. There are new concepts and old controversies such as the role of permissive underfeeding and the optimal timing of nutrient delivery. Glucose control is also one such area where there is still no widespread agreement on optimal targets for blood glucose control in ICU. In addition to modulating the provision of protein / energy delivery, speakers looked at the infl uence of nutrition on blood glucose control and discussed new clinical data suggesting that higher protein – lower carbohydrate enteral nutrition may improve glycaemic control without increasing the risk of hypoglycaemia.

Glycaemic control in critically ill patients: how tight should it be?



Greet Van den Berghe, MD, PhD
Department of Intensive Care Medicine, University of Leuven, Belgium

There is still no widespread agreement around optimal targets for glucose control in the ICU: some clinicians maintain that glucose control is unnecessary and harmful, while others claim that blood glucose control is essential to improve prognosis.[1-3]

Those who favour liberal glycaemic control assert that hyperglycaemia is simply a benefi cial adaptation in critically ill patients to provide fuel for vital organ systems. This view is supported by results from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study which concluded that tight glycaemic control (TGC) led to moderate and severe hypoglycaemia and an increased risk of death.[4]

The other view is that hyperglycaemia, in the context of early nutrition, is maladaptive and harmful. Glucose overload in cells that do not need insulin for glucose uptake may cause mitochondrial damage and, while hypoglycaemia is a risk, it can be prevented.

To explore the relationship between blood glucose levels and prognosis, we carried out two studies, using an identical design, on patients entering either the adult surgical ICU (S-ICU) or adult medical ICU (M-ICU).[5,6] In both studies, patients were randomly assigned to receive intensive insulin therapy (IIT: target maintenance level 80 to 100mg/dL) or conventional treatment (insulin only when blood glucose was between 180 and 215mg/dL and stopped again when falling below 180mg/dL). IV glucose was given on admission, followed on day 2 by early standardised parenteral (PN) combined with enteral nutrition (EN).

Pooling the results for the 2748 patients, IIT was associated with a clear reduction in hospital mortality of 4% (p=0.02) in the total population and 8% (p=0.006) among those patients who were in the ICU for at least 3 days.[7]

It was unclear whether maintenance of normoglycaemia or administration of insulin contributed to the clinical benefi ts but a subsequent animal study suggested that most benefi ts were due not to the administration of insulin but to the avoidance of hyperglycaemia.[8] Glycaemia-independent effects of insulin were evident only when normoglycaemia was maintained.

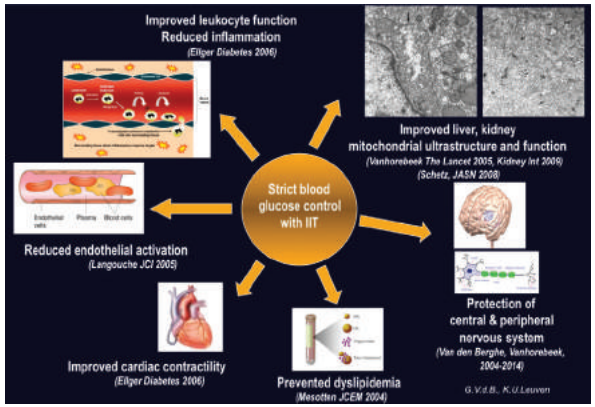
Further studies found that hyperglycaemia brought about cellular glucose overload in the kidney, which was associated with mitochondrial dysfunction and renal injury. Histological examination showed clear fl attening of the tubules with loss of tubular epithelium and intraluminal debris or calcifi cation in kidneys from the hyperglycaemia group.[9] It was also found that hyperglycaemia induced cellular glucose overload in the liver and myocardium, causing mitochondrial dysfunction.[10]

In 7/9 human patients who had been treated conventionally there were enlarged mitochondria in liver samples with increased abnormal and irregular cristae. Only 1/11 patients given intensive insulin therapy displayed these abnormalities (p=0.005).[11] The authors noted that the lack of effect on skeletal muscle mitochondria suggested a direct effect of glucose toxicity rather than of insulinaemia.

Numerous mechanistic studies have confi rmed that cells which are not dependent on insulin for glucose uptake can experience mitochondrial damage from hyperglycaemia in the context of critical illness.

A post hoc analysis of the results from the S-ICU and M-ICU studies found a marked survival benefi t of intermediate vs limited control, and a slight further improvement with tight control, while only tight control produced very marked benefi ts in terms of new kidney injury.5-7 With polyneuropathy, benefi t was only seen with the tightest control.

In children, it is critical to target relevant age-adjusted values; targeting adult fasting levels of glucose may be harmful or, at best, ineffective. Seven hundred critically ill infants and children who



were admitted to the paediatric ICU (PICU) were randomly assigned to target blood glucose levels (2.8 to 4.4mmol/L for infants, 3.9 to 5.6mmol/L for children) with insulin infusion throughout PICU stay, or to a second group where insulin infusion was used only to prevent blood glucose exceeding 11.9mmol/L.[12] BG was brought down to fasting levels in the intensive group and benefi ts of tight control were seen in multiple areas including shorter PICU stay (5.51 vs 6.15 days, p=0.017), lower C-reactive protein (9.75mg/L vs 8.97mg/L, p=0.007) and fewer infections (29.2% vs 36.8%, p=0.034). Hypoglycaemic episodes must be carefully managed to avoid rebound to high glucose levels. A comparison of children who had experienced hypoglycaemic episodes with those who had not, revealed no adverse effects on IQ, visual-motor integration or executive functions.

This contrasts with the fi ndings of the NICE-SUGAR study which reported an increased risk of death in ICU patients who had experienced a hypoglycaemic episode.[4] This was attributed not to any effect on organ function, rather to cardiovascular failure.

Several important differences between the studies need to be highlighted. First, different target levels were used, with the two study arms in the NICE- SUGAR study being much closer together. Compliance levels also differed: in the Leuven studies, 70% of patients in the intervention group achieved target levels compared to less than 50% in the NICE-SUGAR study.

Many of the glucometers allowed in the NICE-SUGAR study have since been found to be unsuitable for their purpose.[13,14] Inaccuracies in measuring glucose can result in poor insulin titration and lead to large BG fluctuations and undiagnosed hypoglycaemia. Further errors could have been introduced through use of a too simple “if-then” algorithm that could be adapted or even set aside, unlike the computerised algorithm that has been developed at Leuven.[15]

Finally, in the NICE-SUGAR study, feeding was almost entirely via the enteral route whereas at Leuven, inadequate enteral feeding was supplemented with PN. It is possible that the NICE-SUGAR feeding protocol induced global substrate deficit through insulin-induced suppression of metabolism. On the other hand, PN in the Leuven studies may have increased the severity of stress-induced hyperglycaemia, with insulin infusion being required to counter the effect.

To investigate this, two RCTs were conducted to compare early vs late PN in critically ill adults (EPaNIC) and children (PEPaNIC).[16,17] Both studies produced similar results, more pronounced in children, with patients experiencing more infections and a lower likelihood for live discharge with early PN. In a secondary analysis it was found that delayed recovery with early feeding was explained by the amount of proteins or amino acids consumed, rather than glucose.[18] The likely mechanism is that amino acids suppress autophagy, a process which eliminates mitochondria that are damaged by hyperglycaemia.

Given these insights, our proposal is to re-do our original randomised controlled studies but under different conditions. In particular we will target fasting blood levels against hyperglycaemia up to 215mg/dL, and will not include early PN. This study, the “TGC-fast” study has received funding and is now in the process of being set up to recruit almost 10,000 patients.

Dysglycaemia in the critically ill

As has been pointed out, the benefits of tight glycaemic control in the ICU have by no means been clearly established or accepted. In 2010 a meta-analysis of seven prospective randomised studies concluded that intensive insulin therapy in mixed ICU patients was not supported by evidence.[19]

Today we understand that hyperglycaemia, hypoglycaemia, and high glycaemic variability are all associated with poor outcomes. A review of 44 studies in the literature reporting hyperglycaemia in over 500,000 ICU patients found an association with many different types of outcomes. Another study on a large database of more than 100,000 patients, demonstrated that hyperglycaemia, hypoglycaemia, and high glycaemic variability all increased the risk of inhospital mortality.[20]

Another large multi-centre study in 45,000 ICU patients found that while hyperglycaemia, hypoglycaemia, and high glycaemic variability were each independently associated with mortality, diabetic status modulated these relations such that patients with diabetes may benefit from higher target glucose ranges than those without diabetes.[21]

What therefore is the best way to manage blood glucose in the ICU?

The digestion and absorption of carbohydrates is a complex sequence of events starting in the mouth with amylase, which breaks starches down into shorter-chain sugars. Dextrins and sucrose are broken down further by specific enzymes, while other enzymes (lactase and maltase) at the brush border of the gut contribute to the breakdown of lactose and the oligosaccharides. The end result is glucose, which passes into cells and is released into the bloodstream.

The different types of dietary carbohydrate, such as monosaccharides, oligosaccharides, or polysaccharides, differ in their speed of absorption. The “glycaemic index” is used as a convenient classification to categorise the speed of absorption.

Regarding enteral nutrition, some diabetes-specific formulas (DSF) are available, which are characterised by a lower percentage of carbohydrates and a higher percentage of lipids than standard formulas. However, rather than the amount of carbohydrate, the key difference is the type of carbohydrate as the formulations are put together to give a lower glycaemic index for the diabetes-specific formulas.

A systematic review of the literature in this area included RCTs which compared DSFs with standard formulas, finding that DSF was more effective in controlling glucose profiles. The requirement for insulin in patients with diabetes was lower when using these DSFs.[22] The authors speculated that this may be due to the type of carbohydrate used in these formulations, which may be more slowly digested and absorbed than in standard formulas. There are not many studies on the role of DSF in the ICU. A small study of DSF

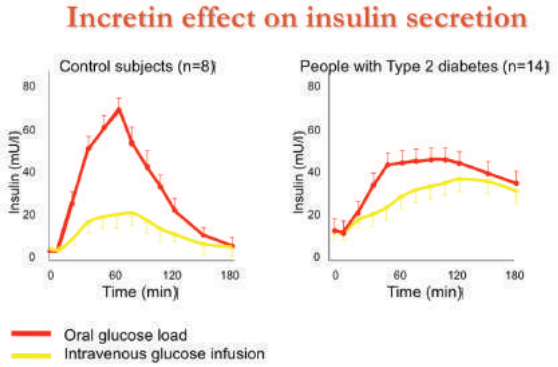
Jean-Charles Preiser, MD, PhD
Department of Intensive Care, Erasme University Hospital, Brussels, Belgium

in hyperglycaemic, mechanically ventilated, critically ill patients assigned around 50 patients to each of three groups, two of which used DSFs while the third used a standard control formula.[23] Insulin requirements were lower in the two DSF groups, while glycaemic control was significantly better.

An important physiological issue that we have to consider in feeding critically ill patients is the incretin effect. Following oral feeding, hormones released by the GI tract will stimulate the pancreas to release insulin. In healthy, non-diabetic subjects, administration of glucose by the IV rather than oral route results in the stimulation of much lower quantities of insulin, as the gut hormones are not produced in the same quantities. In diabetic patients, there is very little difference between the two routes of administration.

A meta-analysis of 13 studies examining the influence of enteral vs parenteral nutrition on glucose control in patients with acute pancreatitis confirmed that PN was associated with an increased risk of hyperglycaemia and therefore an increased requirement for insulin.[24]

In patients receiving continuous enteral feeding, if this is associated with a release of endogenous insulin then the amount of exogenous insulin



needed to maintain a steady blood glucose level would be lower during feeding and higher during interruptions. Hence, the calculated insulin sensitivity would fall when feeding is interrupted and rise when feeding is restarted.

This hypothesis was tested in a group of critically ill, non-diabetic patients for whom records were available, for a minimum of 10 hours of enteral feeding followed by at least 7 hours with an interruption to enteral feeding, and at least 5 hours of resumed EN.[25] Data for 52 of these patients was available and it was found that insulin sensitivity dropped following interruptions to enteral feeding, thereby supporting the presence of an incretin effect.

New guidelines for glucose control were published in 2010 just after the controversy between the Leuven studies and the NICE-SUGAR study.[26] Unfortunately these guidelines reflect the uncertainty and lack of evidence:

regarding carbohydrate intake it is not possible to suggest a general recommendation of maximal or minimal amounts of intravenous or enteral carbohydrates to be administered to critically ill patients regardless of the type, the severity of the pathology and the delay from onset of disease. It is also suggested that hyperglycaemia be reduced by restricting intravenous glucose in critically ill patients.

A pragmatic approach is to begin EN as soon as possible, adapting the infusion rate to the tolerance of the patient, trying to limit caloric debt rather than to achieve full matching of energy expenditure. In some centres, routine clinical practice includes the administration of low doses of IV glucose (50-100g/day) as a maintenance solution. As well as this, the use of dynamic scales for the dosing of insulin and attempts to minimise glycaemic variability are strongly recommended.

Facilitated glucose control in the ICU through nutrition

As recently as 2010, the view of metabolic requirements for patients admitted to ICU was that all patients had the same metabolic needs and could therefore be managed with the same nutritional product. In general, critically ill patients were fed along the same lines as healthy people in the ratio of around 50% carbohydrates, 35% lipids and 15% protein. However, little benefit has been found from this approach or from the strategy of "temporary starvation" to patients in the ICU who cannot otherwise feed.

During starvation, protein is often used as an energy source rather than as an anabolic precursor to muscle synthesis. In the absence of glucose there is a lack of substrate for the formation of pyruvate, which leads to a decrease in the uptake of protein into tissues. Instead dietary proteins are broken down into amino acids to provide an alternative energy source. The goal of medical nutrition therapy in the critically ill is to maximise anabolism, minimise catabolism and minimise oxidation of amino acids.

The way in which patients are fed can have an impact on sugar levels and insulin infusion rates. In the EDEN study, 1000 adults with acute lung injury requiring mechanical ventilation were randomised to receive either trophic or full enteral feeding for the first 6 days.[27] Although the feeding strategy had little effect on mortality, infectious complications and ventilator-free days, the trophic group had lower plasma glucose levels and required lower insulin infusion rates to achieve BG targets.

While energy feeding in critically ill patients has been well studied, until recently little was known about early protein feeding. Insights were provided by a 2014 observational study with 843 mixed medical-surgical critically ill patients who required prolonged mechanical ventilation.[28] Food intake and energy expenditure were closely monitored over four days. It was found that in non-septic, critically ill patients, early high protein intake was associated with lower mortality, and early energy over-feeding with higher mortality. In septic patients, early high protein intake had no beneficial effect on mortality.

The first study to investigate the concept of permissive underfeeding evaluated the effect of restricting non-protein calories compared to standard enteral feeding in 894 critically ill adults while maintaining the full recommended amount of protein in both groups.[29] There was no difference in any of the many clinical outcomes that were measured such as mortality, days free from mechanical ventilation, length of ICU stay and length of hospital stay.

Todd Rice, MD, MSc
Vanderbilt University,
Nashville, Tennessee, USA

We have recently completed a study, as yet unpublished, to determine whether blood glucose control could be facilitated by using an enteral nutrition formula containing a low level of carbohydrates, lower medium chain triglycerides, and very high levels of hydrolysed whey protein, to ensure optimal protein delivery. The DIVINE study was an open label multi-centre randomised trial carried out at seven academic medical centres in the USA. It was planned to enrol 280 patients with the aim of 160 completing five days of enteral nutrition. The study ran for almost two years, from August 2014 through July 2016.

Patients were included if they were mechanically ventilated, critically ill, obese or overweight (BMI 26 to 45), and required enteral nutrition for at least five days. Patients were excluded if they had liver failure, trauma or were planned for major surgery.

A control group was fed a high protein formula with regular amounts of carbohydrate, and the intervention group had a very high protein, low carbohydrate formula.

Both feeds had a caloric density of about 1kcal/ml, but the protein in the experimental group was about 50% higher at 92g/L while the carbohydrates were about a third lower at 76g/L, and the fat content was fairly similar in both groups at 38 and 34g/L. The aim was to deliver 1.5g/kg of ideal body weight per day of protein.

The primary endpoint was the rate of glycaemic events in the first seven ICU days as defined by blood glucose levels outside the interval of 6.1 to 8.3mmol/L. Secondary endpoints included blood glucose, markers

DIVINE: Intervention

- **Control group**: High protein formula
- **Experimental group**: Very high protein, low carbohydrate formula

	Control Group (Replete®)	Experimental Group (Peptamen® Intense VHP)
Caloric Density (kcal/mL)	1.0	1.0
Protein (% energy)	64 g/L (25%)	92 g/L (37%)
Carbohydrate (% energy)	112 g/L (45%)	76 g/L (29%)
Fat (% energy)	34 g/L (30%)	38 g/L (34%)

of nutritional status, urine and serum ketones, insulin and dextrose administered, and clinical outcomes.

One hundred and five patients were randomised (53 control and 52 experimental) and 102 were included in the intention to treat (ITT) analysis. There were 51 patients in each arm. The groups were similar apart from a greater number of women in the control group.

Regarding nutritional intake, the experimental group received significantly fewer calories and carbohydrates than the control group as planned, and both groups received about the same amount of protein. Over the seven days of the study, caloric intake was about 60% of the planned intake in both groups, and slightly more than 60% of the protein target, which was 1.2g/kg compared to the target of 1.5g/kg.

Looking at the primary endpoint, there was no difference between the groups in the rate of glycaemic events outside of the intervals (6.1 to 8.3mmol/L). In the experimental group there was a higher rate of glycaemic events in the normal range of 4.4 to 6.1mmol/L but these are not defined as hypoglycaemic. In the same group there was a lower rate of marked hyperglycaemia (>8.3mmol/L). The mean glucose was lower in the experimental group by almost 1mmol/L (p=0.004). There was no difference in the rates of hypoglycaemia (<4.4mmol/L), and there was a smaller glycaemic dispersion in the experimental group (p=0.0015). There was a significant decrease of 11% in the frequency of insulin administration in the experimental group and there was no difference in the amount of rescue dextrose that had to be used.

There was an increased frequency of abdominal distension in the experimental group, which may have been due to the formula and to intolerance of higher protein levels. Distension was considered to be related to the formula in one case in the control group and one in the experimental, which was withdrawn from one patient. Overall there was no difference between groups in the number of patients with adverse events. Mortality was not significantly different, but was numerically lower in the experimental group with two deaths (4%) compared to six (12%).

To conclude, in the DIVINE study a very high hydrolysed whey protein and low carbohydrate formula facilitated blood glucose control in critically overweight and obese patients. Although the formula did not reduce the incidence of blood sugar events outside the interval of 6.1 to 8.3mmol/L, it did lower the dispersion of blood glucose, resulted in a lower incidence of hyperglycaemia (>8.3mmol/L), increased the incidence of normoglycaemia and decreased insulin use without increased adverse events.

The increased recognition of proteins in critical illness

There are many new concepts and old controversies surrounding nutrition in critical care such as: the role of trophic feeding, permissive underfeeding, the use of immune modulating agents, and the optimal timing of nutrient delivery. However, enteral nutrition and protein delivery have consistently been found to be beneficial.

Traditionally, the concerns in the ICU were about meeting energy requirements while protein levels were rarely considered. Early work carried out in the 1920s by Cuthbertson had largely been forgotten until the 1980s.

Conditions in the ICU result in loss of muscle mass: patients are immobile, often have minimal energy and protein delivery, and undergo little or no resistance exercise.[30-32] Twenty-one days after a single blunt injury, 16% of total body protein is lost, 67% of it from the muscle.[33] Resting energy expenditure (REE) increases progressively over the first week to 40% above normal and can still be elevated after three weeks.

Conventional methods of analysis may not give a true picture of the rate of muscle loss. Ultrasound of the rectus femoris muscle in ICU patients showed a loss of around 10% within 10 days; but biopsies showed a thinning of muscle collagen fi bres by 17.5% and when using a ratio of DNA to cellular protein, a loss of 29.5% is seen.[34] Signifi cant infl ammatory changes in skeletal muscle were observed despite patients being given an average of 0.7g/kg/day of protein.

Muscle loss is not confined to extremity skeletal muscle. A study investigating muscular volumetric changes compared the diaphragm to extremity skeletal muscle and found that there was greater loss of the diaphragm muscle.[35]

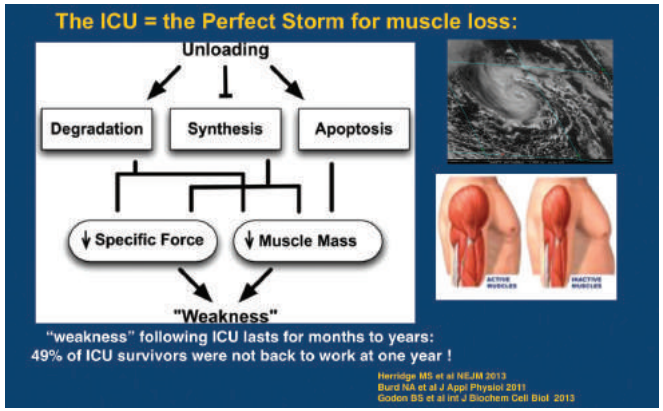
Robert G Martindale, MD, PhD
Oregon Health and Sciences University, Portland, Oregon, USA

A recent study investigating mechanisms of chronic muscle wasting in elderly ICU patients found that most parameters such as proteolysis, autophagy and infl ammatory cells normalised at six months, but satellite cells remained consistently depressed.[36] Satellite cells appear to regulate the ability of muscle to recover from major loss, therefore if these cells are compromised, there is a decreased ability to regenerate muscle. ICU-acquired weakness and muscle wasting has a complex aetiology but increased protein degradation, reduced protein synthesis and often limited protein intake play a part.[37]

The loss of muscle mass is dramatically increased on admission to an ICU. If inadequate protein is not supplied to these catabolic patients muscle lost during hospitalisation may never be regained. It has been reported that short term amino acid infusions improve protein balance and small randomised clinical trials with parenteral nutrition show modest benefi ts in muscle strength and fatigue.[38-41]

Questions still surround the optimal target for protein. There are numerous studies supporting protein delivery in the ICU from 0.8g/kg/day up to 2.5g/kg/day. Large observational studies of ICU patients report most critically ill patients receive around 0.6g/kg/day of protein. Several studies consistently support that the goal for protein delivery should be at least 1.5g/kg/day and possibly higher.[41-45]

There is no consensus as yet on the upper limit. Some clinicians advocate delivery of up to 3g/kg/day (in adolescent patients), but guidelines are generally consistent in recommending an upper limit of 2.5g/kg/day.[46,47]



There are potential issues with excess protein including azotaemia, hepatic protein synthesis and altered mental status which are more theoretical than observed.[48,49]

A number of studies have demonstrated that infusion of exogenous amino acids can improve whole-body protein balance, without increasing amino acid oxidation rates in critically ill patients.[38,50,51] A higher protein intake was generally associated with an improved nitrogen balance, with dosages of 2g/kg/day being more successful than lower intakes.[52]

There is also concern that protein delivery may affect the autophagy balance. Nutrient delivery inhibits autophagy but activates cellular protein synthesis so there is not a simple direct relationship between feeding (or starvation) and autophagy.

Could anabolic resistance be a factor in ICU patients? Anabolic resistance is driven by an insensitivity to the anabolic effects of amino acids, particularly leucine. Although we do not have defi nitive answers for overcoming anabolic resistance we do know that certain approaches, such as hypercaloric PN or EN, hypocaloric feeding, use of anti-infl ammatory, and appetite stimulants do not work. On the other hand we know that certain interventions work consistently to protect lean body mass: protein supplementation, delivered by pulsed bolus; early enteral feeding, which protects the gut barrier and decreases systemic infl ammation; metabolic modulation with nutrients such as leucine, arginine, and specialised pro-resolving molecules (SPMs); glycaemic control, resistance exercise and support for the microbiome. Other interventions appear to work in other patient groups but have not yet been confi rmed as of benefi t in the ICU.

In conclusion, there is good evidence to support protein in the ICU is benefi cial although delivery must be individualised. An upper range of 2.5g/kg/day is considered safe. Optimal protein intake may be different in the acute compared to the prolonged phase of illness. Due to the heterogeneous nature of the ICU population decisions must be made on an individual basis. Aggressive protein delivery combined with resistance exercise may improve muscle kinetics, metabolism and regeneration. Most of our evidence currently comes from observational trials, which may not be consistent with RCTs and there are still many unanswered questions.

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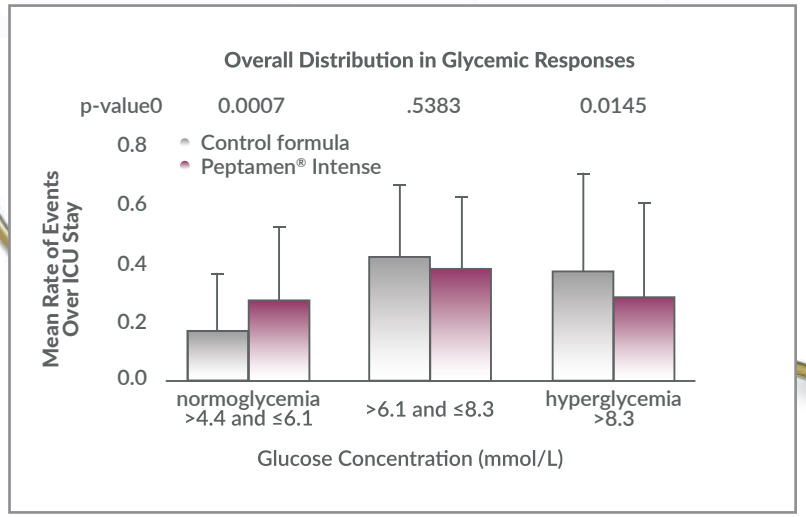

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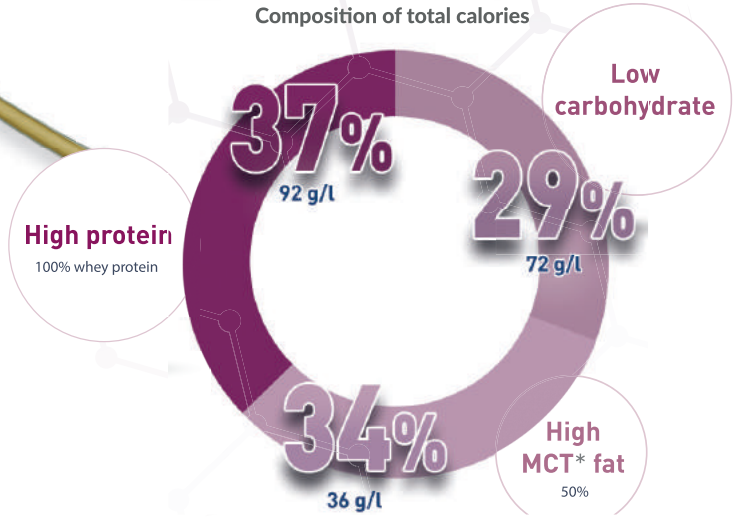

Shown to achieve protein goals without overfeeding ICU Patients [3,4]

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MCT = Medium-Chain Triglycerides

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Luis Morales-Quinteros*
Intensive care physician
Dept. of Intensive Care Medicine
Hospital Universitario Sagrado CorazÛn
Barcelona, Spain

luchomq2077@gmail.com

Marcus J. Schultz
Department of Intensive Care &
Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A)
Academic Medical Center
Amsterdam, the Netherlands

Antonio Artigas RaventÛs
Dept. of Intensive Care Medicine
Hospital de Sabadell

CIBER de Enfermedades Respiratorias
CorporaciÛ Sanitaria I Universit ria Parc Taulì
Sabadell, Spain

ICU Management & Practice Editorial Board Member

* corresponding author

CO^2 in the critically ill

Implications for the intensive care physician

CO_2 exerts potent effects on lung biology that could be clinically relevant in critically ill patients, in particular those with acute respiratory distress syndrome (ARDS). The impact of hypercapnia on outcome in these patients is yet to be determined.

The physiological effects of hypercapnia are increasingly well understood, but the literature remains confusing. Important insights have emerged regarding the impact of hypercapnia on cellular and molecular function. Hypercapnia may have potentially beneficial effects in patients with acute respiratory distress syndrome (ARDS), independent of the benefits from ventilation with low tidal volumes (Broccard et al. 2001; Curley and Laffey 2013), including reduction in pulmonary inflammation (Takeshita et al. 2003) as well as reduced oxidative alveolar damage (Shibata et al. 1998). It has also been suggested that CO_2 can act as a signalling molecule via pH-independent mechanisms resulting in deleterious effects in the lung, all derived from hypercapnia (Briva et al. 2007). Clearly, hypercapnia has potent but potentially beneficial as well as potentially harmful effects. It becomes increasingly important to determine the net effect in specific conditions (Kregenow et al. 2006).

We review the biological and clinical effects of hypercapnia, especially in the patient with ARDS.

Biological effects

Ventilator-induced lung injury (VILI)

Hypercapnia has potential beneficial effects, which have been observed in experimental studies of acute lung injury, such as reduction in the levels of inflammatory mediators or oxidative alveolar damage. However, several studies suggest that CO_2 could exert deleterious effects on the lung, independent of pH levels. The effects of CO_2 on lung tissue are summarised in **Table 1**.

Beneficial effects

Several studies have shown that hypercapnia reduces ventilation–induced damage through its effects on mechanical stretch–induced injury:

1. Improvement of oxygenation, pulmonary elastance and vascular permeability with histological improvement of lung lesions (Halbertsma et al. 2010; Peltekova et al. 2010).
2. Prevention of the activation of the mitogen-activated protein (MAP)-kinases pathway, thus reducing the production of pro-inflammatory mediators (Gillespie and Walker 2001; Pugin 2003; Otulakowski 2014).
3. Reduction of apoptosis, oxidative stress and markers of inflammation by inhibiting the activation of the MAP-kinase and stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) pathways at the level of the alveolar epithelial cells (Yang et al. 2013).
4. Decreased inflammatory response and improvement of pulmonary mechanics by inhibiting the canonical nuclear factor (NF)-κB pathway, degradation of IkB-α and translocation of nuclear p65 into cells (Contreras 2012).

Harmful effects

At the cellular level, hypercapnia delays epithelial and alveolar repair of lung tissue induced by mechanical ventilation through the following mechanisms:

5. Delayed repair of the alveolar membrane by decreasing cellular migration dependent on the NF-κB pathway (Doerr 2005; O'Toole 2009).
6. Decreased clearance of alveolar oedema through inhibition of the Na+ -K+ -ATPase pump through an endocytosis process. This process has been shown to be pH independent (Briva 2007; Welch 2010; Vadász 2012; Lecuona 2013).
7. Suppression of the innate immunity and host defence by inhibiting mRNA and the expressions of

Table 1. Effects of hypercapnia on the lung

Beneficial
Decrease inflammatory response through NFkB pathway inhibition:
• Decrease neutrophil migration
• Decrease pro-inflammatory cytokine release
Deleterious
Alveolar epithelial function:
• Alveolar oedema clearance impairment through Na+/K+- ATPase pump endocytosis
Epithelial cell repair
Innate immunity/host defence

inflammatory cytokines (IL-6 and TNF-α) and autophagy in macrophages (Lang 2005; Oliver 2012).

Effects of hypercapnia in the setting of ARDS

Permissive hypercapnia

Hickling et al. were the first to propose protective ventilation strategies as a rescue therapy for patients with severe ARDS with the aim of limiting VILI (Hickling et al. 1990). These strategies incorporated the following measures: 1) low peak inspiratory pressure and low Vt ventilation; 2) use of positive end-expiratory pressure (PEEP); and 3) acceptance of higher partial pressure of arterial carbon dioxide ($PaCO_2$) levels. Although that study had a series of limitations, the significant difference in hospital mortality in favour of protective ventilation strategies and permissive hypercapnia (16% vs. 39.6%) led to a series of prospective studies of protective ventilation in patients with ARDS. Based on those findings, five prospective randomised clinical trials of protective ventilatory strategies were carried out (Amato et al. 1998; Brochard et al. 1998; Stewart et al. 1998; Brower et al. 1999; Acute Respiratory Distress Syndrome Network 2000). In these studies, two showed a significant reduction in mortality (Acute Respiratory Distress Syndrome Network 2000; Brower et al. 1999) (**Table 2**) of protective ventilation over ventilation with high Vt (12 ml/kg/IBW). Although permissive hypercapnia was present in these studies, there are certain limitations to conclude a protective effect of CO_2, such as high statistical variability, and non-randomisation of patients to receive normocapnia or hypercapnia, since the primary aim of these studies was to investigate the effect of low stretch ventilation in ALI/ARDS.

With the intention to determine whether, in addition to the effect of tidal volume reduction, there may be an independent effect of hypercapnic acidosis, the database of the ARMA trial was re–analysed (Kregenow et al. 2006). It was found that permissive hypercapnia reduced mortality in patients randomised to the higher tidal volume, but not in those receiving lower tidal volumes.

Although the approach of permissive hypercapnia is tempting, high levels of CO_2 are not an easy partner for a patient with ARDS who suffers with low compliance, severe hypoxia, dyspnoea and high respiratory drive, and who requires a certain amount of sedation to allow the ventilator to take over their ventilatory distress.

> "increasingly recognised that CO_2 is much more than a waste product of cellular metabolism"

Recently, in a secondary analysis of three prospective non-interventional cohort studies focusing on ARDS patients in 40 countries including a total of 1899 patients, it was found that severe hypercapnia ($PaCO_2$ > 50 mmHg) was associated with higher ICU mortality compared to patients who kept normocapnia (OR 1.58, CI 95% 1.04–2.41; p = 0.032). Acidosis or the combination of hypercapnia and acidosis were independently positively associated with ICU mortality, as well as barotrauma, renal and cardiovascular dysfunction (Nin et al. 2017).

These findings are in line with those reported by Tiruvoipati et al. (2017). They performed a retrospective analysis including more than 250,000 patients receiving mechanical ventilation. They found that patients who developed hypercapnic acidosis (pH< 7.35 $paCO_2$ > 65 mmHg) during the first 24 hours of mechanical ventilation had a significantly higher mortality than those who had compensated hypercapnia or normocapnia.

Alveolar dead space

In ARDS, the alveolar dead space (VDALV) is particularly interesting. VDALV comes from respiratory units that receive disproportionately low perfusion compared with ventilation (Q < V), resulting in an increase in West Zone 1 physiology. In many patients with ARDS, the disordered pulmonary ventilation-perfusion ratio results from endothelial injury, microvascular plugging with cellular aggregates and thrombi, and disordered pulmonary blood flow, leading to increased alveolar dead space (Tomashefski et al. 1983), decreasing CO_2 clearance. Clinical interest in physiological dead space measurement was reawakened in 2002, linking dead space measurements to prognosis in ARDS (Nuckton et al. 2002). Physiological dead space was measured in 179 mechanically ventilated ARDS patients on the day of the syndrome onset. The mean dead space fraction (VD/VT) was 0.54 in eventual survivors and 0.63 in patients who succumbed to the syndrome, and the risk of death increased with every 0.05 increment in VD/VT. The physiological dead space measurement outperformed all of the previous prognostic measures including traditional measures of oxygenation impairment, lung compliance and illness severity (Nuckton et al. 2002). Unfortunately, in clinical practice, VD/VT measurements are uncommon. We believe that is due to poor understanding of dead space physiology and poor integration of CO_2 waveforms and derived data with other monitoring systems. Based on the arterial CO_2 measurements and predicted mixed expired CO_2 concentrations, Siddiki et al. found that at both day 1 and day 3 of ARDS diagnosis, patients with a V_D/V_T in excess of 0.50 had a risk of death that increased with every additional 0.10 increment in V_D/V_T (Siddiki et al. 2010), a risk prediction that almost exactly equalled the predictive power of the complete CO_2 measurements on ARDS patients described by Nuckton.

Mechanical ventilation: a life-saving procedure that can kill the lung

In the past 20 years, VILI has become one of the most studied topics in critical care (Tremblay and Slutsky 2006), confirming that mechanical ventilation not only damages lung tissue but even contributes to mortality. A major cause of VILI in the past was

ventilation with high Vt, which was used to maintain adequate alveolar recruitment and mean airway pressures (Pontoppidan and Geffin 1972). Although the seminal ARDS Network trial gave the guidelines for ventilation with low Vt, it has been observed that up to 30% of patients with ARDS ventilated with Vt 6 ml/kg (IBW) show alveolar overdistension, generating VILI (Terragni et al 2007). It is worth noting other mechanical ventilator-associated complications such as ventilator-associated pneumonia (VAP), ventilator-associated diaphragmatic dysfunction (VIDD), and a range of neurological disorders associated with prolonged sedation and immobilisation (Melsen and Rovers 2009; Jackson et al. 2011; Jaber et al. 2011).

Extracorporeal carbon dioxide removal: a bright future?

The use of extracorporeal devices to remove CO_2 ($ECCO_2R$) has been evaluated as an adjuvant for protective ventilation, with the aim of reducing Vt levels to values lower than 6 ml/kg (IBW). This strategy is called "ultraprotective ventilation".

Terragni et al., in a study with 32 patients with early ARDS (<72 hours), observed a decrease in the levels of inflammatory cytokines in bronchoalveolar lavage in patients undergoing ultraprotective pulmonary ventilation (Vt close to 4 ml/Kg IBW) + $ECCO_2R$, showing less damage induced by mechanical ventilation (Terragni et al. 2009).

The Xtravent study did not observe an impact on mortality in patients with ARDS undergoing ultraprotective ventilation + $ECCO_2R$. However, a post hoc analysis of the group of patients with $PaO_2/FiO2<150$ showed a decrease in mechanical ventilation days in patients who received ultraprotective ventilation (Vt 3 ml/kg IBW + $ECCO_2R$) (Bein et al. 2013).

Recently the EuroELSO working group carried out a systematic review of current clinical experience with extracorporeal CO_2 removal in the critically ill (Taccone et al. 2017). They included only studies with a proper control group (studies comparing extracorporeal CO_2 removal to standard treatment). Six case-control trials with a total of 279 adult patients (142 treated with $ECCO_2R$) were identified: three of them were performed in COPD patients with hypercapnic respiratory failure and three in ARDS patients; only two trials were randomised, both in ARDS patients, in which $ECCO_2R$ was applied to allow ultraprotective ventilation. No study was sufficiently powered to disclose an effect on relevant clinical outcomes such as ICU length of stay or mortality. The overall quality of the studies was low, with a high methodological bias, not allowing any conclusion to be drawn on the clinical effectiveness of $ECCO_2R$ in critically ill patients.

Study	Mortality Benefit	$PaCO_2$ Standard Mechanical ventilation (mm Hg, mean ± SD)	$PaCO_2$ Lung Protective Ventilation (mm Hg, mean ± SD)	Buffering Permitted
ARDSNet 2000	Yes	35.8 ± 8.0	40.0 ± 10.0	Yes
Amato et al. 1998	Yes	36.0 ± 1.5	58.0 ± 3.0	No
Stewart et al. 1998	No	46.0 ± 10.0	54.5 ± 15.0	No
Brochard et al. 1998	No	41.0 ± 7.5	59.5 ± 19.0	No
Brower et al. 1999	No	40.1 ± 1.6	50.3 ± 3.5	Yes

Table 2. Ventilatory strategies and management of CO_2 in clinical trials

The Strategy of UltraProtective Lung Ventilation With Extracorporeal CO_2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA) trial (**clinicaltrials.gov/ct2/show/NCT02282657**), which has completed its first pilot recruitment of patients with moderate ARDS undergoing ultraprotective ventilation + $ECCO_2R$, will show more data on the use of extracorporeal CO_2 removal in this group of patients. In addition, a randomised clinical trial, pRotective vEntilation With Veno-venouS Lung assisT in Respiratory Failure (REST) is underway to observe 90-day mortality in patients with hypoxaemic acute respiratory failure who undergo ultraprotective ventilation with $ECCO_2R$ (**clinicaltrials.gov/ct2/show/NCT02654327**).

To date, the available literature does not have enough evidence to make clear recommendations for the use of this technique in the critical patient, and its use is currently experimental.

Should we use a buffer to treat acidosis?

The use of a buffer to treat hypercapnic acidosis remains a common clinical practice, although it is controversial.

The justification for its use is the physiological effects associated with extreme levels of hypercapnic and metabolic acidosis (pH < 7.10) (Forsythe and Schimdt 2000; Kraut and Madias 2010). In particular these are myocardial contractility depression and haemodynamic instability refractory to catecholamine infusion, in addition to the effects of acidosis on the central nervous system and the immune function, as well as metabolism reduction.

Specific concerns exist regarding sodium bicarbonate ($NaHCO_3$), the buffer used most frequently in the clinical setting. Although the physiochemical effect of $NaHCO_3$ is to increase the strong ion difference, the net effect is the generation of CO_2, therefore $NaHCO_3$ is an inappropriate therapy in patients with hypercapnic acidosis.

Tromethamine (THAM: tris-hydroxy-metylaminomethane) has been considered a better choice of buffer. THAM, by diffusing easily into cells, corrects pH and simultaneously reduces carbon dioxide levels. By increasing pH levels, THAM could mitigate the adverse effects of acidosis produced on the cardiovascular system and restore haemodynamic stability (Weber et al. 2000). However, it does not solve the problem of underperfused regions of the lung, which remain under severely alkalotic conditions, or control the $PaCO_2$ in patients with high dead space (Pesenti and Patroniti 2010).

Future directions

It is increasingly recognised that CO_2 is much more than a waste product of cellular metabolism. Indeed, it is a potent biological agent that exerts multiple effects. Although the protective effects of CO_2 have been observed in multiple models of acute lung injury, hypercapnia also exerts meaningful harmful effects. There is a clear need for robust evidence from well–powered RCTs to determine whether hypercapnia adds to or subtracts from the benefits of ventilation with low lung volumes and distending pressures.

$ECCO_2R$ may be a promising adjuvant therapeutic strategy for the management of patients in order to achieve protective or ultra-protective ventilation in patients with ARDS without life-threatening hypoxaemia. However, difficulties in predicting the progression of disease at an early stage may limit its use in clinical practice.

It would be interesting to analyse the impact of hypercapnia on outcome not only in the different forms of ARDS (mild, moderate and severe), but also to look at the impact of CO_2 in patients at low and high risk for ARDS, and how they move from different stages according to CO_2 levels and V_D/V_T, consider the causes of hypercapnia and target the ideal $PaCO_2$ to best balance the favourable and unfavourable biological effects of hypercapnia.

Conflict of interest

Luis Morales-Quinteros declares that he has no conflict of interest. Marcus J. Schultz declares that he has no conflict of interest. Antonio Artigas Raventós declares that he has no conflict of interest. ■

Abbreviations

ARDS acute respiratory distress syndrome

IBW ideal body weight

JNK Jun amino-terminal kinases

MAP mitogen-activated protein

NF-κB nuclear factor-κB

$PaCO_2$ partial pressure of arterial carbon dioxide

SAPK stress-activated protein kinases

VILI ventilator-induced lung injury

Vt tidal volume

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Improving diagnostic stewardship by using new microbiological technologies

A case report

Describes an episode of sepsis in a leukaemia patient, whose treatment was early guided by using rapid diagnostics technology to identify the cause of infection.

Nieves Larrosa
Clinical Microbiologist
Microbiology Department
Vall d'Hebron University Hospital
Microbiology Research Group
Vall d'Hebron Research Institute
Assistant Professor
Universitat Autònoma
de Barcelona
Barcelona, Spain

mnlarrosa@vhebron.net

Juan José González-López
Clinical Microbiologist
Microbiology Department
Vall d'Hebron University Hospital
Microbiology Research Group
Vall d'Hebron Research Institute
Assistant Professor
Universitat Autònoma
de Barcelona
Co-Director, Sepsis Bank-Vall d'Hebron Hospital
Vall d'Hebron University Hospital
Barcelona, Spain

jjgonzal@vhebron.net

A 4-year-old patient under treatment for acute lymphoblastic leukaemia, diagnosed 6 months before, was admitted to the emergency room (ER) at midnight (00h33) due to a fever episode of less than one hour of evolution in the context of neutropaenia (absolute neutrophil count 400 cel/µL) and without an increase in acute phase reactants (C-reactive protein [CRP] 0.1 mg/dL and PCT 0.34 ng/dL).

During the child's stay in the ER, peripheral blood cultures, peripheral quantitative blood cultures and quantitative blood cultures taken through a Port-a-Cath® implantable venous access system ("port"), were obtained at 1h45. At that time, empiric treatment with piperacillin-tazobactam and amikacin was started. The port was manipulated 6 days earlier to administer the chemotherapy treatment. Additionally, a urine and a pharyngo-tonsillar sample were cultured. In the following hours, the general state of the patient worsened. He showed sustained fever, tachycardia, hypotension, signs of peripheral hypoperfusion, presence of lactic acid levels of 3.3 mm/L in the gasometry and an increase of the acute phase reactants (CRP 15 mg/dL and PCT 46 ng / dL). Consequently, the sepsis code was activated (10h47), piperacillin-tazobactam was replaced by meropenem and vancomycin, and the patient was transferred to the intensive care unit.

The peripheral blood culture was positive at 13h14 (day 1), and at the Gram stain, Gram-negative bacillus was observed. Blood cultures were processed according to the standard routine workflow of the laboratory (fast subculture, MALDI-TOF identification and antibiogram by VITEK®2 system), and also with the Accelerate Pheno™ system using the Accelerate PhenoTest™ BC kit. The Accelerate Pheno™ system returned an identification of *Escherichia coli* after 1.21 hrs (15h50 on day 1) and an antibiogram 5.17 hours after identification (21h07 on day 1). The *E. coli* isolate was susceptible to all antibiotics evaluated. Consequently, the doctor on call de-escalated the treatment of the patient to piperacillin-tazobactam. The antibiogram performed by the standard technique was obtained at dawn, being informed early in the morning of the following day (day 2). The results of this antibiogram were consistent with those previously obtained by the Accelerate Pheno™ system on day 1. The peripheral quantitative blood culture was positive on day 2, yielding > 500,000 cfu of *E. coli*, and the peripheral quantitative blood taken through the port yielded 40 cfu (ratio of ≥4:1), confirming that sepsis arose from the infected port. Urine and pharyngo-tonsillar cultures were negative. On day 2, given the good clinical evolution, the child was transferred back to the onco-haematology ward, following removal of the port.

Conclusions

The time to obtain laboratory results needed to diagnose certain pathologies has been reduced by the application of technological innovations. This is essential in clinical situations in which fast and accurate results can translate into significant benefit for patients, increasing survival rates and improving health outcomes. Currently, rapid microbiologic diagnosis of bacteraemia and consequently of sepsis is limited by the difficulty of making a rapid and direct diagnosis from the patient's blood. The blood cultures are still necessary, and in most cases, clinicians must wait 24h-36h to have the final identification and antimicrobial susceptibility of the causative agent.

"Accelerate Pheno™ system allowed us to obtain the information about the infecting pathogen and its susceptibility testing in less than 24h since the patient was admitted to the hospital"

Several studies have shown that 30% to 50% of antimicrobial treatments are inappropriate or unnecessary

in terms of treatment indication, choice of antimicrobial agent and incorrect duration of antibiotic therapy. In this sense, the diagnostic stewardship professes to guide the therapeutic decision by microbiological results. To do this, it is necessary that the laboratory communicates an accurate and a timely pathogen identification and antimicrobial susceptibility testing. In the case described herein, the Accelerate Pheno™ system allowed us to obtain information about the infecting pathogen and its antimicrobial susceptibility in less than 24h from the patient's admission to the hospital—sooner than when a conventional approach was used. This permitted the clinician to select the most appropriate antibiotic sooner than would be possible when following our standard laboratory workflow. Likewise, the reduction in the time to antibiotic de-escalation, from empiric treatment with meropenem and vancomycin to piperacillin-tazobactam, reduced the potential for selection of multi-drug resistant bacteria during treatment. ■

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Immune dysfunction in sepsis

Diagnostic and treatment options

An overview of the recent advances in the diagnosis and treatment of immune system dysfunction in sepsis.

Velma Herwanto*
PhD candidate
Nepean Clinical School
University of Sydney
Sydney, Australia

Department of Intensive Care Medicine
Nepean Hospital, Sydney, Australia

Centre for Immunology and Allergy Research
Westmead Institute for Medical Research, Sydney, Australia

vher6289@uni.sydney.edu.au

Marek Nalos
Senior Staff Specialist
Nepean Clinical School
University of Sydney
Sydney, Australia

Department of Intensive Care Medicine
Nepean Hospital, Sydney, Australia

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016). Sepsis-induced immune system dysfunction is an important sequelae of sepsis. The persistence of immune system dysfunction in the later stages of sepsis increases patients' susceptibility to secondary infections and, consequently, leads to an increased mortality (Boomer et al. 2011; Torgersen et al. 2009; Zorio et al. 2017; Cavassani et al. 2010). In recent years, there have been major advances in the research of sepsis-induced immune dysfunction. The purpose of this article is to review how these recent advances could be translated into future, better ways of diagnosing and treating immune system dysfunction in sepsis patients.

Diagnosis of immune system dysfunction

A myriad of immune deficits has been identified in sepsis patients. Here we describe the major immune deficits that can be measured by either well-established biomarkers or readily available laboratory methods. While the evidence base for these measurements remains incomplete, the methods listed below represent some of the most promising advances made in recent years.

1. HLA-DR

What has the research shown?

Expression of monocytes HLA-DR has been shown to be a useful biomarker of immune dysfunction (Monneret et al. 2008). HLA-DR is a major histocompatibility complex (MHC) class II cell surface receptor found on antigen presenting cells. Its role is to present peptide antigen to elicit T helper response. Low mHLA-DR levels have been associated with a higher risk of developing nosocomial infections and a higher mortality in sepsis patients (Landelle et al. 2010; Monneret et al. 2006; Caille et al. 2004).

What is the diagnostic method?

Monocytes HLA-DR can be measured by flow cytometry; however, this remains problematic due to high inter-laboratory variance (25%) (Docke et al. 2005).

2. PD-L1 and PD-L2

What has the research shown?

Programmed death-1 (PD-1) and its associated pathway negatively control immune responses. Up-regulation of the PD-1 gene (in T cells) and its ligands, PD-L1 and PD-L2 (antigen presenting cells) may impair adaptive immune response. Overexpression of these molecules has been shown to correlate with increased secondary nosocomial infections and adverse outcomes in septic patients (Zhang et al. 2011; Guignant et al. 2011).

What is the diagnostic method?

Specific monoclonal antibody binding to PD-L1 and PD-L2 and flow cytometry analysis can be used.

3. Cytokines

What has the research shown?

Measuring either pro- or anti-inflammatory cytokines may aid the diagnosis of immune dysfunction. For example, increased anti-inflammatory cytokine IL-10 production was associated with reduced expression of HLA-DR and PD-L1 on monocytes and PD-1 on T-cells (Guignant et al. 2011).

What is the diagnostic method?

Commercially available assays for detection and analysis of cytokines are the enzyme-linked immunosorbent assays (ELISA), the enzyme-linked immune spot (ELIspot) assay, and the polymerase chain reaction (PCR) method to determine gene expression for cytokine production. For better evaluation of the complex inflammatory response, researchers can use multiplex-based immunoassays, such as the bead-based immunoassay read by flow cytometer or micropatterned antibody cytokine array (Stenken and Poschenrieder 2015). As another alternative, intracellular cytokine staining (by flow cytometry analysis) has also been used in some studies (Monneret and Vennet 2016).

4. Immunoglobulin

What has the research shown?

Hypo-gammaglobulinaemia has been a frequent finding in patients with sepsis. Low levels of immunoglobulin isotypes (IgG, IgA, IgM) has strongly correlated with prognosis (Tamayo et al. 2012; Prucha et al. 2013).

What is the diagnostic method?

Quantitative serum immunoglobulin tests are used to detect abnormal levels of the three major classes (IgG, IgA and IgM). Among the tests available, nephelometry and turbidimetry are the most widely used methods because of their speed, ease of use and precision (Loh et al. 2013).

5. Lymphocytes

What has the research shown?

Lymphocytes from septic patients have been found to be anergic, i.e. lacking the late-phase hyper-reactivity in the intradermal tests. This "anergic" state was associated with an

Anthony S. McLean
Professor of Intensive Care Medicine
Nepean Clinical School
University of Sydney
Sydney, Australia

Director
Department of Intensive Care Medicine
Nepean Hospital, Sydney, Australia

Benjamin Tang
Associate Professor in Intensive Care Medicine and Head of Genomic Research Group
Nepean Clinical School
University of Sydney
Sydney, Australia

Department of Intensive Care Medicine
Nepean Hospital, Sydney, Australia

Centre for Immunology and Allergy Research
Westmead Institute for Medical Research, Sydney, Australia

*corresponding author

increased vulnerability to secondary infections and mortality (Christou et al. 1995). Septic T cells also demonstrated a low proliferation rate in vitro (Lederer et al. 1999). However, as proliferation tests require a long incubation time, they are not routinely performed (Monneret et al. 2011).

What is the diagnostic method?

Lymphocyte counts may reflect immune cell apoptosis in sepsis (Cheadle et al. 1993; Rajan and Sleigh 1997). Lymphopaenia following the diagnosis of sepsis or persistent lymphopaenia may therefore serve as a biomarker for immune dysfunction (Drewry et al. 2014; Parnell et al. 2013).

6. Signature gene-expression markers

What has the research shown?

HLA-DR mRNA gene expression may be a valuable diagnostic tool to overcome the methodological difficulties with flow cytometry described earlier (Le Tulzo et al. 2004; Monneret et al. 2004; Cajander et al. 2015). In addition, anti-apoptotic Bcl-2 gene expression in patients with sepsis has been shown to be associated with a reduced T-cell count and may also be used as a marker of immune dysfunction (Bilbault et al. 2004). Other potential gene-expression biomarkers, such as T-bet, GATA-binding protein 3 (GATA3), CTLA-4, PD-1, PD-L1, PD-L2, CD47, CD3, CD28 and LAG-3, were also associated with changes in the $CD4^+$ T cell response in sepsis patients (Zhang et al. 2011; Guignant et al. 2011; Roger et al. 2009; Hotchkiss and Karl 2003; Venet et al. 2005).

What is the diagnostic method?

These markers can be measured by real-time PCR, which is available in most hospital laboratories.

7. Host response "endotypes"

What has the research shown?

Recent transcriptomic analysis of the peripheral blood of sepsis patients revealed two distinct sepsis response signature (SRS) groups, termed "SRS1" and "SRS2" by the authors of the study (Davenport et al. 2016). The presence of SRS1 (detected in 108 [41%] patients) identified individuals with an immunosuppressed phenotype that included features of endotoxin tolerance, T-cell exhaustion, and downregulation of HLA-DR. The SRS1 group had a higher 14-day mortality with a hazard ratio of 2.4 (95%CI 1.3–4.5). There were similar findings from a more recent transcriptomic study, in which the study authors used a 140-genes signature to stratify sepsis patients into four endotypes. One endotype was associated with a higher 28-day mortality in septic patients, with a hazard ratio of 1.86 (95% CI 1.21-2.86) (Scicluna et al. 2017). Both these studies indicated that sepsis "endotypes" (distinctive gene clusters of immune pathways) correlate with the degree of immune dysfunction and adverse outcomes in sepsis patients.

> "immune modulation therapy needs to be sufficiently broad to correct immune defects in sepsis, but also be titratable to prevent untoward immune system activation"

What is the diagnostic method?

Whole genome transcriptomic analysis (using peripheral blood samples) can be used to measure sepsis endotypes in patients.

Treatment of immune system dysfunction

Ideally, the immune modulation therapy needs to be sufficiently broad to correct the widespread immune defects in sepsis, but at the same time must be titratable to prevent untoward immune system activation. Personalised immune profiling, as outlined in the previous section, will allow clinicians to titrate the immune therapy and correct any inadvertent alterations in immune defence.

Next, we will highlight several previously studied therapies as well as therapies that are currently in the development stage;

1. Established immune modulating agents

One of the oldest immune modulating agents is the cytokine IFNγ. In a seminal study, Docke et al. (1997) reported that IFNγ administered to septic patients with low monocyte HLA-DR expression on monocytes restored HLA-DR expression and resulted in clearance of sepsis in eight of nine patients. Since then, a relatively small number of septic patients have been treated with IFNγ, including those with persistent staphylococcal and invasive fungal infections (Delsing et al. 2014; Nalos et al. 2012). However, there is no randomised controlled trial data available for IFNγ.

Another cytokine that has been studied is a haematopoietic growth factor granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF therapy reversed defective TNFγ response, T-cell anergy and prevented nosocomial or recurrent infections in children. In adults, GM-CSF treatment restored HLA-DR expression on monocytes, and reduced secondary infections and duration of hospital stay (Rosenbloom et al. 2005; Orozco et al. 2006). Meisel and colleagues tested the efficacy of GM-CSF in patients with decreased monocyte HLA-DR expression (Meisel et al. 2009). Additionally, a clinical trial (GM-CSF to Decrease ICU Acquired Infections - GRID trial) evaluating this therapeutic approach in septic shock patients is soon to be completed (**clinicaltrials.gov/ct2/show/NCT02361528**).

IL-7 is another potential therapeutic agent, with recombinant human cytokine IL-7 (rhIL-7) being investigated for sepsis immunotherapy. Treatment with rhIL-7 demonstrated improved T cell proliferation, enhanced lymphocyte metabolism and IFNγ production ex vivo in septic patients (Venet et al.

2017; 2012). Based on these promising results, a phase 2 multicentre randomised controlled trial (IRIS trial) assessing rhIL-7 in patients with septic shock was designed (A Study of IL-7 to Restore Absolute Lymphocyte Counts in Sepsis Patients (IRIS-7-B) - **clinicaltrials.gov/ct2/show/NCT02640807**); its primary aim is to ascertain the safety and ability of rhIL-7 to increase the absolute lymphocyte count in immunosuppressed septic patients.

"the complexity of sepsis-induced immune dysfunction is now being unravelled by rapid advances in the "omics" sciences"

2. New immune modulating agents

CTLA-4, PD-1, PD-L1 and LAG-3 are potent immune cell inhibitors that are highly upregulated in septic patients. Immune checkpoint inhibitors are antibodies, originally used in cancer treatment, that target these key signalling pathways. These include anti-PD-1 antibodies (nivolumab and pembrolizumab) and anti-PD-L1 antibodies (atezolizumab, avelumab and durvalumab). These agents have been shown to reverse the exhausted cytotoxic T cells in cancer patients, thereby restoring T cell function; therefore, this approach may be a promising therapeutic strategy in sepsis (Chang et al. 2014; Zhang et al. 2010). Ex vivo studies using cells from septic patients' cells have shown that a PD1/PD-L1 pathway blockade decreased sepsis-induced immune dysfunctions (Chang et al. 2014; Zhang et al. 2010). However, immune checkpoint inhibitors could cause autoimmune adverse events, which are driven by the same immunologic mechanisms responsible for their therapeutic effects. Serious and life-threatening autoimmune events are reported in the literature with treatment-related deaths of up to 2% of cancer patients (Puzanov et al. 2017).

Thymosin alpha-1 (Ta1), and Flt3L protein are molecules that can induce appropriate dendritic maturation and T cell activation (Flohé et al. 2006). In septic animals, Flt3L increased dendritic cell numbers and IL-12 production in these cells, thus enhancing CD8 T cells responses (Strother et al. 2016). A recent report demonstrated the efficacy and safety of recombinant human Flt3L (Anandasabapathy et al. 2015). Ta1 also induces the maturation of dendritic cells and T cells maturation. In a recent meta-analysis, Li et al. (2015) evaluated the results of twelve controlled trials using Ta1 in sepsis and found a trend towards lowering all-cause mortality. Clearly, further studies are needed to explore the therapeutic potential of these molecules.

Summary

The complexity of sepsis-induced immune dysfunction is now being unravelled by rapid advances in the "omics" sciences (e.g. transcriptomics). In the near future, novel biomarkers will be used to measure specific immune deficits in sepsis patients. Furthermore, promising immune therapies (e.g. checkpoint inhibitors) are also currently being investigated in pre-clinical studies. Validation of these new diagnostics/therapeutics in a clinical trial setting will be an important next step. ■

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Conflict of interest

Velma Herwanto, Marek Nalos, Anthony S. McLean and Benjamin Tang declare that they have no conflict of interest.

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Hypothermia in neurocritical care patients other than cardiac arrest

Hypothermia (HT) is a cornerstone of neuroprotective strategies and has been used in critical care for acutely brain injured adult patients for many years. This review aims to discuss the clinical evidence supporting the use of HT in neurocritical care patients beyond care after cardiac arrest (CA), such as traumatic brain injury (TBI), acute ischaemic stroke (AIS), non-traumatic intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). Despite promising results in small clinical trials and laboratory studies, HT did not improve outcome in large multicentre trials. Similarly, the use of HT as a specific intervention to treat secondary brain damage failed to improve outcome in humans. Despite these negative results, targeted temperature management (TTM) remains a crucial intervention in neurocritical care as part of the emerging principle of individualised medicine. Based on the pathophysioloy of harmful effects associated with fever, the concept of normothermia has been implemented in most neurointensive care units to prevent periods of fever. In the following we will review the current status of HT as well as ongoing clinical trials of TTM (see summary in Table) and provide some thoughts for designing future studies.

Raimund Helbok*
Associate Professor of Neurology and Neurocritical Care
Head of Neurocritical Care Research Group / Neuromonitoring
Department of Neurology
Neurocritical Care Unit
Medical University of Innsbruck
Innsbruck, Austria

raimund.helbok@tirol-kliniken.at
raimund.helbok@i-med.ac.at

Ronny Beer
Associate Professor
Department of Neurology
Neurocritical Care Unit
Medical University of Innsbruck
Innsbruck, Austria

* corresponding author

From a conceptual point of view, mild HT (32–34°C) can be used as prophylactic intervention early after acute brain injury (ABI) or as a symptom-based treatment for e.g. refractory intracranial hypertension, brain oedema, vasospasm after SAH and other complications. If HT is used as specific therapy it is important to first prove that the resolution of such complications is in fact associated with improved functional outcomes before an intervention like HT with potential detrimental side effects is implemented. Though experimental data suggest a significant neuroprotective effect for TTM, large multicentre clinical trials investigating HT in ABI failed to demonstrate an unambiguous clinical benefit.

Hypothermia as early prophylactic neuroprotective treatment

Traumatic brain injury

TBI is a dynamic disease with distinct pathophysiologic mechanisms depending on the injury type, injury severity and the time elapsed since the initial trauma (Maas et al. 2017). Secondary injury mechanisms including excitotoxicity, neuro-inflammation, ionic fluctuations, necrosis and apoptotic cell death have been well characterised in preclinical studies. Most of these factors are sensitive to temperature changes and may be aggravated by intracranial or extracranial insults. HT has been used in the treatment of TBI for many years and can effectively ameliorate secondary injury. Despite promising results from experimental studies and small clinical trials (Polderman 2008), large multicentre trials failed to translate the putative benefits of HT into improved outcome in TBI patients (Clifton et al. 2001; 2011; Maekawa et al. 2015). A trend towards improved functional recovery was seen in TBI patients who were hypothermic on admission, suggesting that ultra-early initiation of HT may be important (Clifton et al. 2001). In the National Acute Brain Injury study: Hypothermia II (NABISH II) trial mean time to 35°C was reached after 2.6h and time to 33° was 4.4h (Clifton et al. 2011). However, enrolment was stopped for futility when interim analyses found no difference in mortality or neurological outcomes. Post-hoc analysis suggested a benefit for severe TBI patients with focal lesions undergoing haematoma removal, pointing to the pathophysiologic concept of reperfusion injury that may be ameliorated by HT (Clifton et al. 2012). The Hypothermia for Patients requiring Evacuation of Subdural Hematoma (HOPES) trial is currently investigating this hypothesis in TBI patients requiring emergent craniotomy (**clinicaltrials.gov/ct2/show/NCT02064959**). Based on the concept of ongoing secondary injury beyond 48h after severe TBI, long-term HT (4-6 d) was associated with significantly higher rate of favourable outcomes at 6 months when compared to short-term HT (1-3 d) in a single-centre trial including 215 severe TBI patients with cerebral contusion and intracranial hypertension (Jiang et al. 2006). Extended cooling over 5 days is currently explored in the Long-term Mild Hypothermia for Severe Traumatic Brain Injury (LTH-I) trial (**clinicaltrials.gov/ct2/show/NCT01886222; Lei et al. 2015**). In addition, the POLAR-RCT (Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury) trial aims to investigate the effect of early (prehospital) and sustained (72 h) mild HT on 6 months neurological outcomes in severe TBI patients, and titrates rewarming speed to intracranial pressure (ICP) and mean arterial pressure (MAP) (**clinicaltrials.gov/ct2/show/NCT00987688**); (Nichol et al. 2015).

Current Brain Trauma Foundation guidelines recommend against the use of early (within 2.5h), short-term (48h post-injury) prophylactic hypothermia in severe TBI patients with diffuse injury (Level IIB; **braintrauma.org**). Despite a large

Table. Characteristics of selected ongoing clinical TTM trials in patients with acute brain injury **(clinicaltrials.gov)**

To Study the Effect of Early Cooling in Acute Subdural Hematoma Patients (HOPES) **clinicaltrials.gov/ct2/show/NCT02064959**	
Status	Recruiting
Inclusion criteria	Non-penetrating traumatic brain injury
	Glasgow Coma Scale (GCS) motor score ≤5 (not following commands)
	Estimated or known age 22-65 years
	Acute subdural haematoma requiring emergent craniotomy within 6 hours of initial injury
	Estimated time of injury to time to reach temp. of 35°C<6 hrs
Study arms	Hypothermia (33°C)
	Standard care - normothermia (37°C)
Primary outcome	Glasgow Outcome Scale-Extended (GOSE) at 6 months
Randomized Controlled Trial of Long-term Mild Hypothermia for Severe Traumatic Brain Injury (LTH-I) **clinicaltrials.gov/ct2/show/record/NCT01886222**	
Status	Recruiting
Inclusion criteria	Age 18 - 65 years within 6 hours post injury
	Closed head injury
	GCS score 4 to 8 after resuscitation
	The intracranial pressure is more than 25 mmHg
	Cerebral contusion on computed tomographic scan
Study arms	Long-term mild hypothermia (34-35°C for 5 days)
	Normothermia (36-37°C)
Primary outcome	Glasgow Outcome Scale (GOS) at 6 months
The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT) **clinicaltrials.gov/ct2/show/NCT00987688**	
Status	Recruiting
Inclusion criteria	Blunt trauma with clinical diagnosis of severe TBI and GCS <9
	Estimated age ≥ 18 and < 60 years of age
	The patient is intubated or intubation is imminent
Study arms	Early and sustained hypothermia (3°3C for 72 hours)
	Normothermia (37°C ± 0.5°C)
Primary outcome	Favourable neurological outcomes 6 months (GOSE 5 to 8)
Safety and Feasibility Study of Targeted Temperature Management After ICH (TTM-ICH) clinicaltrials.gov/ct2/show/NCT01607151	
Status	Unknown
Inclusion criteria	Spontaneous supratentorial ICH documented by CT scan within 18 hours after the onset of symptoms
	Admission to the Neuro-ICU
	Baseline haematoma >15cc with or without IVH
	Need for mechanical ventilation
Study arms	Hypothermia for 72h (32-34°C)
	Normothermia for 72h (36-37°C)
Primary outcome	Severe adverse events at 90 days
Impact of Fever Prevention in Brain Injured Patients (INTREPID) **clinicaltrials.gov/ct2/show/NCT02996266**	
Status	Recruiting
Inclusion criteria	Admitted with a primary neurological diagnosis of ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage
	Prior to onset of acute symptoms, was considered functionally independent (mRS 0-2)
	Meets disease-specific criteria
Study arms	Prophylactic normothermia
	Standard care
Primary outcome	Fever Burden [Time Frame: Up to 14 days]

number of studies, there remains no high-quality evidence that prophylactic hypothermia is beneficial in the treatment of patients with severe TBI (Lewis et al. 2017).

Acute ischaemic stroke

In AIS mild HT is not effective to salvage neural tissue that has progressed irreversibly to infarction. HT can be directed at minimising the extent of secondary injury in the acute or subacute period of AIS. Based on animal data HT has a huge potential as a neuroprotective strategy when used early (within 2-3h), and mitigates ischaemic and reperfusion damage even when initiated up to 6 hours after ictus. However, clinical studies are limited by low patient numbers, slow recruitment, methodological issues and the occurrence of complications such as pneumonia and shivering, especially during HT in awake patients. So far, unequivocal efficacy of HT (33–35°C) has not yet been shown in AIS patients (Lyden et al. 2016; Piironen et al. 2014; De Georgia et al. 2004; Hemmen et al. 2010; Ovesen et al. 2013; Bi et al. 2011; Els et al. 2006), and the use outside clinical studies can currently not be recommended (Jauch et al. 2013; Ntaios et al. 2015).

The Cooling Plus Best Medical Treatment Versus Best Medical Treatment Alone for Acute Ischaemic Stroke (EuroHYP-1) trial explores the value of HT (34–35°C for 24h) within 150 minutes after start of alteplase administration and within 6 hours after stroke onset (van der Worp et al. 2014). The primary outcome is the degree of disability at 3 months measured by ordinal regression analysis of the modified Rankin Scale. This trial aims to recruit 800 patients and has recently reported safety based on preliminary analysis of 62 patients.

Intracerebral haemorrhage

Despite evidence from animal studies that HT attenuates perihaematoma oedema, inflammation and thrombin-induced injury and preserves blood-brain barrier integrity in ICH, we lack human data demonstrating improved neurologic outcome secondary to these beneficial effects of HT (Fischer et al. 2017). Two observational studies showed that mild prolonged HT (35°C over 8–10 d) had a favourable impact on perihaematomal oedema and ICP. However, no benefit for neurologic outcome was observed (Kollmar et al. 2010; Staykov et al. 2013). Although slow recruiting, the CINCH trial investigates HT at 35°C for 8 days in patients with primary ICH and large haematoma volume (25–64 mL) (Kollmar et al. 2012). A phase II prospective trial investigating 72h of mild HT (32–34°C) compared to normothermia (36–37°C) aims to include 50 supratentorial ICH patients (volume >15 ml) (**clinicaltrials.gov/ct2/show/NCT01607151**). For now, prophylactic mild HT is considered investigational in ICH patients and should only be applied in clinical trials (Hemphill et al. 2015). There is a strong need for prospective randomised-controlled trials further investigating the effect of hypothermia on perihaematoma oedema progression and neurological outcome.

Subarachnoid haemorrhage

Hypothermia has been used already in the 1950s as a neuroprotective strategy during aneurysm surgery in SAH patients (Botterell et al. 1956). The IHAST trial investigated HT (33°C) compared to normothermia in 1001 good-grade SAH patients during aneurysm surgery and failed to demonstrate an outcome benefit (Todd et al. 2005). Based on the reported non-significant increase in recovery, a recent Cochrane review, summarising 3 studies with 1158 participants, argued that it remains possible that intraoperative HT may be beneficial in good-grade SAH patients (Li et al. 2016). No conclusions can be drawn for poor-grade SAH patients.

Prophylactic HT was mostly tested in poor-grade SAH patients in single-centre studies underpowered to detect a difference in functional outcome (Choi et al. 2017; Gasser et al. 2003; Seule et al. 2009). An observational matched controlled study including 36 poor-grade SAH patients investigated early (<48h after ictus), mild (35°C), and prolonged (7±1 days) HT, and found a decreased rate of macro-vascular vasospasm and delayed cerebral ischaemia (DCI) (Kuramatsu et al. 2015). In a recent systematic review and meta-analysis including 9 studies the authors found a significant reduction in DCI favouring HT without an overall effect on mortality and morbidity (Yao et al. 2018). Further trials powered to detect differences in clinical outcomes are needed to investigate the potential role of HT after SAH in greater detail.

Hypothermia as symptom-based intervention (to treat raised ICP)

HT was beneficial in controlling raised ICP and improving outcome in single-centre studies; however, large multicentre trials including the recently published Eurotherm3235 trial failed to confirm these findings for a heterogeneous TBI patient population (Andrews et al. 2015). This trial examined the effect of moderate HT (32–35°C) on ICP and neurological outcome and found that titrated HT successfully reduced ICP but did not improve functional outcome at 6 months. Interestingly, there were fewer occurrences of failure of stage 2 interventions to control ICP in the HT group, and stage 3 interventions (i.e. barbiturate coma but not decompressive craniectomy) were more often used in the control group. These data support the effectiveness of HT in reducing raised ICP. The recently published French guidelines recommend considering TTM at 34–35°C to lower ICP in TBI patients with refractory intracranial hypertension (Grade 2+) (Cariou et al. 2017). Based on expert consensus, TTM at 35-37°C may also be considered in patients with ICH and SAH to lower ICP (Cariou et al. 2017).

Adverse effects associated with hypothermia

Moderate HT is a reasonably well tolerated intervention when patients are meticulously managed in an intensive care environment by experienced clinicians. Vigilant monitoring for laboratory abnormalities, cardiac monitoring and standard critical care guidelines for monitoring of infections are recommended (Madden et al. 2017). Shivering is a physiologic thermoregulatory response and is related to increased metabolism, oxygen consumption, and increased energy expenditure, which could nullify the neuroprotective benefits of TTM. Therefore routine assessment (Badjatia et al. 2008) and aggressive treatment is recommended (Choi et al. 2011; Madden et al. 2017). Another important issue in the use of therapeutic HT is the rewarming phase. It has been shown that rapid rewarming is associated with worse outcome and rebound ICP increase (Schwab et al. 2001; Jiang et al. 2006). In order to avoid this detrimental complication patients with ABI should be rewarmed to normothermia as slowly as indicated on a case-to-case basis (Polderman and Andrews 2011).

Normothermia

Acutely brain-injured patients commonly demonstrate periods of fever during the first few days after admission. Post-injury fever is associated with longer ICU stays and worse outcomes through aggravation of secondary brain injury mechanisms including excitotoxicity, increased oxygen consumption, pro-inflammatory response and increased vascular permeability leading to oedema formation with elevated ICP, increased ischaemic injury and cerebral vasospasm (Kilpatrick et al. 2000). Badjatia et al. reported a reduction in poor neurologic 12 months outcome after SAH in a case control study comparing aggressive temperature control to normothermia and conventional management of fever (Badjatia et al. 2010). Post-hoc analysis of the Japanese Brain Hypothermia (B-HYPO) study suggested a survival benefit of fever control in severe but not critical trauma patients pointing to the concept of normothermia, i.e. avoiding fever in TBI patients (Hifumi et al. 2016). Prophylactic interventions targeting normothermia have been shown to decrease the fever burden, and have been proven safe in haemorrhagic and ischaemic stroke patients (Broessner et al. 2009), and are currently under investigation in a prospective trial targeting 1176 patients (INTREPID trial, **clinicaltrials.gov/ct2/show/NCT02996266**). The goal of normothermia, avoiding fever, and aggressively treating fever has been suggested based on a systematic review in TBI patients and is recommended by a French expert panel reviewing the evidence for TTM in neurocritical care patients using the GRADE method (Madden and DeVon 2015; Cariou et al. 2017). TTM is therefore implemented in most neuro-intensive care units including AIS and TBI to prevent periods of fever (Rincon et al. 2014).

Summary and future perspective

The failure to translate the beneficial effect of HT observed in experimental studies to patients with ABI may reflect a limited knowledge of the multiple pathophysiologic mechanisms of secondary injury in the diverse brain pathologies. In this respect, multimodal neuromonitoring, although still mostly invasive, may help to provide insight into the pathophysiologic consequences of these conditions (Schiefecker et al. 2015). For example, increased brain temperature has recently been associated with cortical spreading depolarisations (CSD) in patients with TBI and spontaneous ICH (Schiefecker et al. 2017; Hartings et al. 2009). This is of interest because it is well known that the occurrence of CSD is extremely energy demanding and contributes to cortical

lesion development following ABI (Hartings et al. 2017). This is further corroborated by the observation that clustered CSD were associated with metabolic distress and oedema development in patients with large ICH (Helbok et al. 2017). Considering the notable progress achieved by incorporating such a multimodal neuromonitoring system, this may open up the opportunity for providing individualised treatment and precision medicine in severely brain-injured patients in the future.

Conclusion

Based on the current evidence the use of prophylactic HT is not recommended in ABI patients (not considering patients with cardiac arrest) and should only be applied in the setting of clinical trials. There is a role for HT as a symptom-based intervention to e.g. treat refractory intracranial hypertension. Further research is needed to characterise the magnitude and duration of temperature modulation after ABI required for improvement of neurologic outcome. Prevention of fever and aggressive fever treatment (i.e. concept of normothermia) is feasible and recommended by experts.

Conflict of interest

Raimund Helbok received speaker 's honoraria of BARD Medical and ZOLL Medical and serves in the advisory board of the Intrepid trial (Bard Medical). Ronny Beer declares no conflict of interests. ■

Abbreviations

ABI acute brain injury
AIS acute ischaemic stroke
CA cardiac arrest
CSD cortical spreading depolarisations
HT hypothermia
ICH intercerebral haemorrhage
IVH intraventricular haemorrhage
SAH subarachnoid haemorrhage
TBI traumatic brain injury
TTM targeted temperature management

Reference

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

Intracranial pressure monitoring devices

Shashank Patil
Consultant
Department of Emergency Medicine
Chelsea and Westminster Hospital NHS Foundation Trust
London, UK

Senior Clinical Lecturer
Kings College London

Shashank.patil@chelwest.nhs.uk

@shashankal1

Fiqry Fadhlillah
Core Trainee EM-Year 3
Department of Emergency Medicine
Chelsea and Westminster Hospital NHS Foundation Trust
London, UK

Fiqry.fadhlillah@nhs.net

Intracranial pressure (ICP) monitoring is the cornerstone for treatment and management of patients, especially following traumatic brain injury (TBI) but also other clinical conditions such as non-traumatic bleeds, hydrocephalus, space-occupying lesions and cerebral oedema. The key target to monitor and treat ICP is to optimise the cerebral perfusion pressure (CPP). CPP is obtained by calculating the difference between the mean arterial blood pressure (MAP) and the ICP [CPP= MAP-ICP].

There is an association between increased ICP and increased mortality in patients following TBI. This can be due to a decrease in CPP which leads to cerebral ischemia or due to herniation of brainstem secondary to expanding volume in the brain. The latter phenomenon was described in the late 18th century, known as the Monroe-Kellie hypothesis.

The other key component to maintain an optimum CPP is the MAP, which determines the cerebral blood flow (CBF). The CBF is controlled by an autoregulatory process which ensures a constant, optimum CPP, even if there is a variation in the MAP. An insult or injury to the brain not only increases the ICP but also affects the autoregulatory process which affects the CBF, together which affects the CPP.

There are various goal-directed therapies to control the raised ICP and maintain an optimal MAP; therefore it is essential to have a monitoring system, which should help guide these interventions. Currently, there are no universally accepted guidelines and hospitals have developed local policies to monitor ICP (Raboel et al 2012). The following section looks at various devices available to monitor ICP.

ICP monitoring

The current recommended gold standard technique to measure ICP is invasive. However, it is important to visit other modalities, which can be broadly classified into noninvasive and invasive methods.

Noninvasive methods

In a recent review (Zhang et al. 2017) noninvasive ICP monitoring was divided into five categories (**Table 1**). This section will review some key noninvasive techniques which are established and can be used in the emergency and acute settings.

Transcranial Doppler

Technique

Transcranial Doppler (TCD) ultrasound is performed using a 2-MHz phased array ultrasound probe and obtains information regarding tissue motion and blood flow velocities (**Figure 1**). This is Doppler sonography and when combined with tissue imaging it is called duplex sonography. The four common acoustic windows in the adult skull are the temporal, orbital, suboccipital and submandibular (Bathala et al. 2013). The views help to determine flow velocities of vessels involved in cerebral circulation (**Table 2**).

The TCD most commonly is measured at the middle cerebral artery (MCA). The Doppler calculates the pulsatality index (PI) in cerebral vessels which then is put in a formula to give calculated ICP. There are several indications to perform TCD. In a recent review (Lau et al 2017) four key areas were reviewed:

1. Diagnosis of midline shift
2. Vasospasm (post sub-arachnoid haemorrhage)
3. Intracranial pressure
4. Cerebral circulatory arrest (brain death)

There are currently several limitations to measure ICP using TCD; some of them are mentioned below (Lau et al 2017).

- TCD PI correlation to ICP has a wider confidence interval when compared to directly invasive ICP monitors.
- Decreased $PaCO_2$ or increased arterial blood pressure can independently influence PI and CBF.
- Patients on extracorporeal membrane oxygenation (venous-arterial) and left ventricular assist devices will have a low flow state and hence it will be impossible to calculate PI and therefore ICP interpretation.

> "future intracranial pressure monitoring should be, ideally, noninvasive, able to give continuous readings and to be used in outpatient settings"

Optic nerve sheath diameter (ONSD)

Technique

The optic nerve is surrounded by dura mater; any rise in ICP leads to increase in size of the ONSD. This can be measured by performing an ocular sonography. A high frequency linear ultrasound probe is placed on the closed upper eyelid, 3mm behind the globe at an axis perpendicular to the optic nerve. The measurements are made in sagittal and transverse plane and then averaged **(Figure 2)**. ONSD varies with gender but is not influenced by age, weight and height. The mean ONSD measurement for men was 3.78mm compared to 3.60mm in women (Sinha et al. 2017). The ONSD expansion can be compared to papilloedema, but unlike papilloedema, ONSD expansion occurs within seconds of an acute rise of ICP (Sinha et al 2017).

The systematic review by Sinha et al. (2017) looked at various aspects of ONSD which can help determine ICP and its diagnostic utility in patient following cardiac arrest (CA).

- An ONSD of 5.7mm corresponded to an ICP >20mm Hg (sensitivity=74%, specificity=100%).
- It has a good diagnostic accuracy when compared with invasive monitoring for detecting an ICP >20mm Hg

- An ONSD <5.4mm was an indicator of survival with a favourable neurological outcome (Glasgow outcome scale of 4 or higher), sensitivity 83%, specificity 73%, positive likelihood ratio 3.1 and negative likelihood ratio of 0.23
- In the post resuscitation period ONSD measured on Day 1, 2 and 3 was significantly higher in non survivors compared to survivors. (7.2mm vs 6.5mm, P=0.008)
- An increase of every 1mm above 5.5mm was associated with a significant increase in mortality (odds ratio 6.3, P=0.03)

ONSD measurements based on ocular sonography is an accurate, noninvasive technique for detection of ICP performed by an experienced operator, but internal institutional validation of optimal ONSD for ICP detection may be required (Rajajee et al 2011).

Infrared pupillometry

Technique

This is more useful to measure cerebral function and cerebral perfusion. Quantitative pupillometers use infrared light to measure pupillary size, amplitude and velocity. The pupillary light response (PLR) leads to pupillary constriction, but a noxious stimulus may elicit a pupillary reflex dilatation (PRD). An analysis can be performed by using variables such as latency of onset, maximum amplitude, reflex duration, and constriction and dilatation velocities.

The PLR is affected by diminished CBF and therefore useful to measure the CBF. It can be used during CPR or even in the post resuscitation phase, as the vaso-active drugs may affect the pupillary size but the PLR is under the influence of the Edingar-Westphal nucleus which is supplied by the posterior cerebral circulation (Sinha et al. 2017).

- Behrends et al. (2012) showed that presence of PLR during CPR at any point was associated with early survival from CA (p=0.0002)
- The absence of PLR >5mins during CPR was associated with poor neurological outcome

Table 1. Noninvasive ICP monitoring methods

Category	Methods
Fluid dynamic	Magnetic resonance imaging Transcranial Doppler ultrasonography Cerebral blood flow velocity Near-infrared spectroscopy Transcranial flight-of-light
Ophthalmic	Spontaneous venous pulsations Venous ophthalmodynamometry Optical coherence tomography of retinaOptic nerve sheath diameter Pupillometry
Otic	Sensing tympanic membrane displacementOtoacoustic emissions/ acoustic measure and transcranial acoustic signals
Electrophysiological	Visual evoked potentials Electroencephalogram
Others	Skull vibrations Brain tissue resonance Jugular vein

Table 2. TCD views and vessels

TCD views	Cerebral vessels
Trans-temporal	Middle cerebral artery Anterior cerebral artery Posterior cerebral artery Posterior communicating artery
Trans-orbital	Ophthalmic artery Internal carotid artery
Suboccipital	Vertebral artery Basilar artery
Submandibular	Distal cervical internal carotid artery

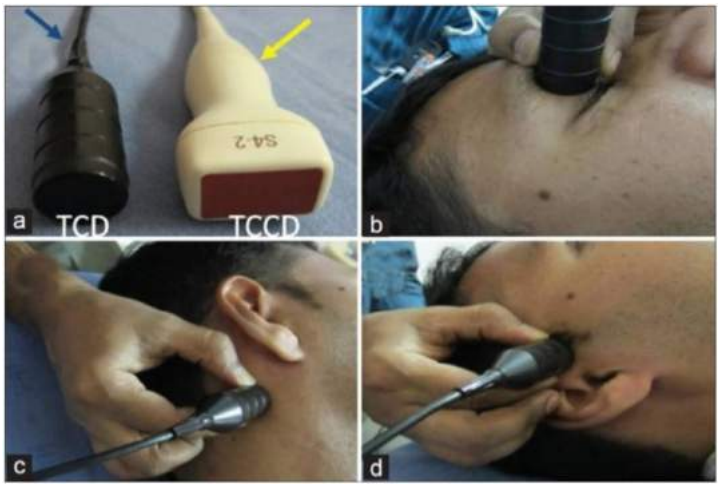

Figure 1. Transcranial Doppler probes and position

Raised ICP is calculated by the Goslingís PI, which is a reflection of peripheral resistance.

PI= Peak systolic velocity ñ Peak diastolic velocity
Mean Velocity

The formula to correlate PI to ICP in clinical practice was derived by (Bellner et al 2004) .

ICP= (10.93 x PI) ñ 1.28

Figure 2. Ocular sonography - probe position

Table 3. Invasive methods of ICP monitoring

Methods	Advantages	Disadvantages
External ventricular drainage (EVD)	Gold standard for ICP measurement; CSF drainage, CSF sampling and administration of drugs; in vivo calibration/control ability; inexpensive	Invasive and challenging insertion High infection rate Occlusion of catheter Sensor repositioning if head is moved False reading if CSF leakage
Lumbar puncture	Extracranial procedure Easy technique to release CSF for therapy	May reflect only instantaneous and not average high ICP May be hazardous if CSF flow obstruction is present and ICP is high
Epidural and Subdural device	Easy to insert; doesn't penetrate the brain, lower risk of infection compared to EVD	Low accuracy Drift of sensor over time In vivo calibration not possible Cannot drain or sample CSF
Intraparenchymal device (fibreoptic or strain gauge)	Insertion and handling simpler than EVD Lower complication rate than EVD Easy patient transport Minimal artefact and rift High waveform resolution Low risk of infection	Inaccurate if Intraparenchymal gradient present Cannot be recalibrated after placement, unless an EVD is used simultaneously for reference. Cannot drain or sample CSF Potential breakage of fibreoptic cable High cost

Source: Reprinted by permission from Zhang X et al.(2017) Invasive and noninvasive means of measuring intracranial pressure: a review, Physiol Meas, 38(8): R143-R182. Published 24 July. https://doi.org/10.1088/1361-6579/aa7256

- Suys et al. (2014) showed higher PLR in CA survivors with better neurological outcome compared to poor outcome measured on cerebral performance category (CPC) score

Invasive methods

Invasive measurement of ICP is the current recommended standard. This can be measured by inserting a catheter into the various anatomical locations of the brain which are determined by the technique: intraventricular, intraparenchymal, subdural, epidural and subarachnoid. The first two techniques are widely used and recommended. ICP can also be measured by lumbar puncture for patients with communicating CSF pathways (Zhang et al. 2017). The Brain Trauma Foundation in their latest updated edition looked at the influence of ICP monitoring on patients' outcome following traumatic brain injury (TBI). It gives a Level II recommendation to use ICP monitoring for management of patients with severe TBI to reduce in-hospital and 2-week post-injury mortality. It also highlighted variability in ICP monitoring approaches between high and low-income countries, which may involve clinical assessment only (Brain Trauma Foundation 2016).

Technique

The standard technique is an invasive procedure that involves catheter insertion into the intracranial compartment through a burr hole. Depending on the position and type of catheter inserted its functionality changes. An extra-ventricular device (EVD) compared to the intraparenchymal device has a higher rate of infection, bleeding or malfunction, obstruction and malposition. **Table 3** lists various methods of invasive ICP monitoring (Zhang et al. 2017).

Telemetric ICP measurement

There has been a non-commercialised attempt to create a system which has long term usability, sensors which do not have wires exiting out of the body and have wireless communication to outside with a limited drift potential. These microelectromechanical types of devices can help measure the ICP. The telemetric way is invasive with the risk limited to implantation of the probe only. It can be left in for several months and can monitor ICP under normal daily living conditions in outpatient settings. However, this technology is not yet reliable and cannot be implemented in clinical practice.

Conclusion

ICP monitoring is a very important clinical tool in clinical practice to determine brain function. It has been established from several studies that continuous ICP monitoring following severe brain injury can help dictate the management and positively influence the final outcome of the patients. There is lack of universal guidance and significant variability in practice around use of ICP monitors and brain pressure monitoring. The current recommended invasive techniques are associated with significant complications; however, noninvasive techniques are available but not widely used. The current situation does highlight a need for integrating ICP monitoring into a multimodal and individualised approach to clinical care. Future ICP monitoring should be, ideally, noninvasive or at least less invasive with minimal complications, able to give continuous readings and to be used in outpatient settings. ■

Abbreviations

CBF cerebral blood flow	MAP mean arterial pressure
CPP cerebral perfusion pressure	ONSD optic nerve sheath diameter
EVD extra-ventricular device	TBI traumatic brain injury
ICP intracranial pressure	TCD Transcranial Doppler

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Complications of decompressive craniectomy in neurological emergencies

A brief report

There are a number of complications related to the use of decompressive surgery. The most important thing to bear in mind is these complications can impair recovery.

Isabel Gonz·lez
Attending Physician
Intensive Care Unit
Complejo Hospitalario De LeÛn
Altos de Nava
Spain

migonzalezpe@saludcastillay-leon.es

What is a decompressive craniectomy?

Decompressive craniectomy is a surgical procedure where a large section of the skull is removed and the underlying dura mater exposed. Primary decompressive craniectomy refers to leaving a large bone flap out after extraction of an intracranial haematoma in the early phase post-TBI. Cranial reconstruction is undertaken between a few weeks and months later with autologous bone (the removed bone flap is stored in the patient's abdominal wall or a deep freezer) or an implant (titanium or other synthetic material). A secondary decompressive craniectomy is used as part of tiered therapeutic protocols that are frequently used in intensive care units (ICUs) in order to control raised intracranial pressure and ensure adequate cerebral perfusion pressure.

What complications are attributable to a decompressive craniectomy?

1. Herniation of the cortex through bone defect
2. Subdural/subgaleal effusion
3. Syndrome of the trephined (headache, dizziness, irritability, mood swings and behavioural disturbance)
4. Seizures
5. Hydrocephalus (defined as dilatation of the ventricular system with accompanying clinical features that required shunt placement).
6. Infection
7. Paradoxical herniation

What complications are attributable to a subsequent cranioplasty?

1. Infection
2. Bone flap resorption

Can the skull defect cause neurological dysfunction?

Certain patients are particularly susceptible to neurological signs and symptoms relating to the presence of a large skull defect. Clinical presentation can range from symptoms such as headaches, seizures, mood swings, and behavioural disturbances (syndrome of trephined) to neurological deficits due to cortical dysfunction (syndrome of the sinking scalp flap).

> "symptoms of paradoxical herniation may be masked and evenmistaken for neurological damage from the trauma"

The pathophysiology responsible for the neurological manifestations has yet to be established. A number of different theories have been put forward, i.e. direct effects of atmospheric pressure on the brain, alterations in cerebrospinal fluid hydrodynamics, and changes in cerebral blood flow and metabolism.

Given the wide variety of clinical manifestations, the mechanism may be multifactorial.

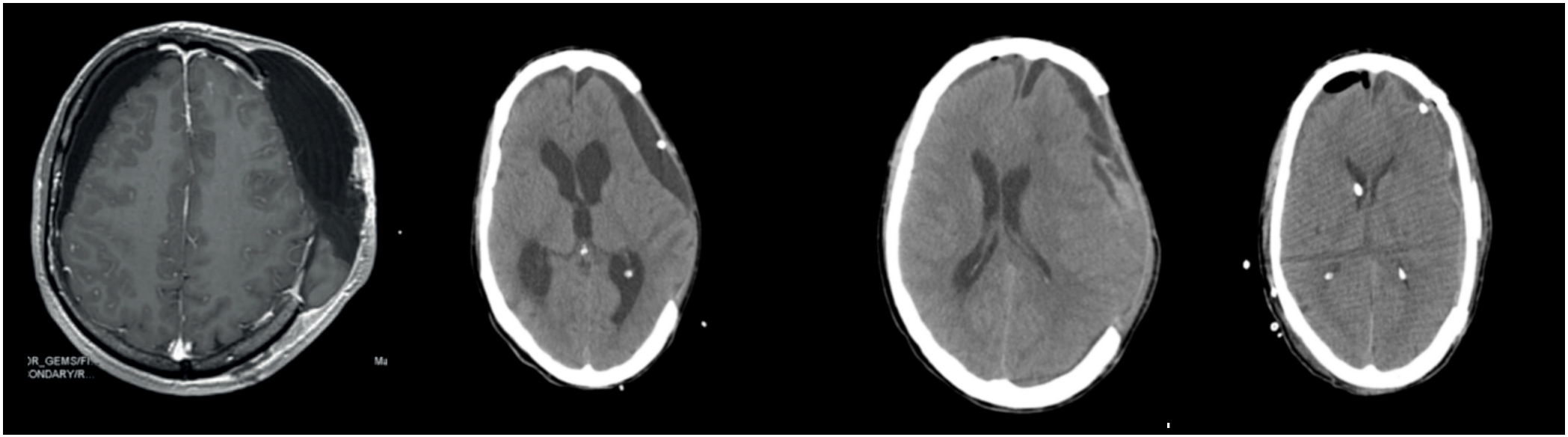
The images correspond to the same patient who presented all the possible complications of a primary decompressive craniectomy after traumatic brain injury: subdural effusions or hygromas, hydrocephalus, paradoxical herniation, seizures, syndrome of trephined, and infection. The final image demonstrates the result after cranioplasty and ventriculoperitoneal shunt and decompressive catheter inside the subdural hygroma.

The most important thing to bear in mind is that we usually see these complications in the ICU. Moreover, we must be very clear about the approach to follow. It is essential to know the probability of neurological deterioration after lumbar puncture or lumbar cerebrospinal fluid (CSF) drainage in the setting of large cranial defects, since this has been observed following decompressive craniectomy and is due to symptomatic herniation.

In the early stage of recovery from traumatic brain injury following decompressive craniectomy, symptoms of paradoxical herniation may be masked and even mistaken for neurological damage from the trauma.

How to avoid complications

Neurosurgeons, intensive care specialists and the other professionals involved in the treatment of these patients need



to carefully decide who will benefit from immediate decompressive craniectomy and who are best treated by initial monitoring and medical treatment of intracranial hypertension. Correct selection for decompressive surgery is required in order to avoid an intervention that increases survival at the expense of a persistent vegetative outcome.

In addition to using the appropriate surgical technique, the patient's neurological condition should be followed closely, looking out for signs and symptoms of syndrome of the trephined.

Tapping and shunt treatment of CSF subdural hygromas should be avoided, where possible. There is also a risk of paradoxical herniation in those patients with a skull defect, who undergo lumbar puncture and ventriculoperitoneal shunt.

A cranioplasty procedure is necessary when the patient is clinically improved. Nevertheless, it is best performed as early as possible, since atmospheric pressure may cause local vascular dysfunction.

Conclusions

Despite the successes and worldwide application of decompressive craniectomy, the procedure remains controversial and there continue to be uncertainties regarding its appropriate application. These areas of controversy can be grouped into four categories: patient selection, timing, technical considerations, outcome results and complications. In this article I have only described the complications.

To what degree patients are affected by the symptoms of syndrome of the trephined is difficult to determine, since many patients are in the severe head injury recovery phase.

Several studies have demonstrated that hydrodynamic abnormalities present prior to cranioplasty were reversed after the bone flap was replaced. In some cases, this was accompanied by a clinical improvement. However, this was not always so.

Technically speaking, whilst the procedure is straightforward, the complications can impair recovery. Not least it represents an aggressive intervention associated with significant morbidity, not only from the initial decompression but also from the subsequent reconstructive cranioplasty.

The aim of this brief review is to emphasise that although decompressive surgery is indicated in some neurocritical patients for cerebral oedema management, the technique is not without significant complications. Furthermore, said complications are not always reversible, and may contribute to a worsening of the neurological outcome of these patients. ■

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Supporting the patient innovator

Developing a novel communication device for tracheostomy patients in the intensive care unit

Their inability to communicate effectively whilst he had a tracheostomy on the intensive care unit (ICU), had such a profound impact on Duncan Buckley and his wife, Lisa-Marie, that they developed a concept for a novel interactive communication device, called 'ICU CHAT'. Together, they have been embedded within the multidisciplinary ICU research team at the Queen Elizabeth Hospital Birmingham (QEHB), supported by the Human Interface Technologies team from the University of Birmingham, and funded by the National Institute of Health Research Surgical Reconstruction and Microbiology Research Centre, to further develop their prototype for clinical trial.

"In our experience (Duncan & I), we found it very frustrating to not be able to communicate in any way with each other and staff. I made a cardboard alphabet board which helped but it was extremely long winded and in itself frustrating to work with."

Lisa-Marie Buckley: Wife of Duncan, University Hospitals Birmingham (UHB) ICU survivor.

Fiona Howroyd
Senior Physiotherapist
Team Leader
University Hospitals Birmingham NHS Foundation Trust
Birmingham, UK

Fiona.Howroyd@uhb.nhs.uk

@fihowroyd

Their inability to communicate effectively whilst he had a tracheostomy on the intensive care unit (ICU), had such a profound impact on Duncan Buckley and his wife, Lisa-Marie, that they developed a concept for a novel interactive communication device, called 'ICU CHAT'. Together, they have been embedded within the multidisciplinary ICU research team at the Queen Elizabeth Hospital Birmingham (QEHB), supported by the Human Interface Technologies team from the University of Birmingham, and funded by the National Institute of Health Research Surgical Reconstruction and Microbiology Research Centre, to further develop their prototype for clinical trial.

Communication in the ICU

Patient communication in the ICU is a widely recognised challenge, causing frustration for patients, relatives and staff (ten Hoorn et al. 2016). Due to the presence of artificial airway devices, such as a tracheostomy, patients are often voiceless as airflow bypasses the vocal cords and inhibits speech. This is often combined with the profound weakness or injury associated with critical illness, therefore limiting other non-verbal forms of communication, such as writing or lip-reading (Muthuswamy et al. 2014). 'Voicelessness' is considered to have both short- and long-term consequences for the patient, including stress, anxiety and social isolation, which are predisposing traits of post-traumatic stress amongst ICU survivors (Wade et al. 2012). It is therefore necessary that methods of communication are developed in order to improve the patient experience in the ICU in addition to patient outcomes.

"this early translational research demonstrates the ability of clinical and academic teams to support potential patient innovators"

Augmented and alternative communications (AAC) devices in the ICU

AAC is a broad term for any method, technology or tool used to overcome barriers to communication. Although there are a range of AAC devices available on the market, none of those identified in the literature have been designed specifically for use in the ICU and therefore have limited transferability to this complex and challenging environment (ten Hoorn et al. 2016). Low technology AAC, such as alphabet boards, are often easily accessible and low cost. However, despite their convenience, low-tech AAC have variable success depending on the physical and cognitive ability of the patient recovering from critical illness and the time constraints and skill of staff (Patak et al. 2004). High technology AAC is a broad and advancing area, yet the available literature identifies practical and financial limitations to use in the ICU (ten Hoorn et al. 2016). The current literature does not explore factors relating to AAC requirements or usability specifically for alert and transiently voiceless tracheostomy patients in the ICU.

Patient-centered design process

The novel 'ICU CHAT' software design, developed by Duncan and Lisa-Marie, has been developed for use by ICU tracheostomy patients, with restricted upper limb function. The use of facial gestures enables the user to control an on-screen cursor with their head movement, selecting phrases with vocal output. This novel and exciting idea was immersed by the Human Interface Technologies team from the University of

Birmingham, alongside the ICU multidisciplinary research team at QEHB. By combining usability assessment with multidisciplinary team qualitative appraisal, the appropriateness of the system components were developed to ensure safety, practicality and low cost for use in the ICU. Following a human-centred design process and rigorous bench testing, the ICU CHAT device was developed (BSI 2010; IEC 2007).

ICU CHAT feasibility study

The multidisciplinary ICU research team at QEHB developed a clinical trial protocol to evaluate the usability and user acceptance of 'ICU CHAT' by patients, staff and relatives at QEHB's ICU. The mixed methods trial design aims to collect quantitative data on usage and performance alongside qualitative appraisal to explore user experiences. The trial *Feasibility of the use of a novel interactive communication device, ICU-CHAT, for patients with tracheostomy on the ICU* has secured Health Research Authority permissions and is open to recruitment at QEHB. This early translational research demonstrates the ability of clinical and academic teams to support potential patient innovators, whose reflections on experiences during their ICU stay enable technology development to be truly patient-centered. ■

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The critical care resuscitation unit

A new paradigm for optimising inter-hospital transfer of patients with non-trauma time sensitive critical conditions

Lia I. Losonczy[1,2,3]

Thomas Scalea[1,4]

Jay Menaker[1,4]

The number of clinical conditions which have improved outcomes associated with shorter time to specialised resuscitation and definitive intervention continues to increase. Many of these time-sensitive conditions have improved outcomes at high volume centres, but these centres are also challenged by limited intensive care unit (ICU) availability to reliably accept patients within optimal time windows. The University of Maryland Medical Centre/R Adams Cowley Shock Trauma Center (UMMC/STC) is a regional referral centre for complex critically ill and injured patients. To optimise care for non-trauma critically ill persons with time-sensitive high-risk conditions, we created an innovative unit, the Critical Care Resuscitation Unit (CCRU), that combines the pace and throughput of emergency departments with the depth and breadth of critical care intervention usually only available at specialty-specific academic intensive care units.

The CCRU provides resuscitative critical care that spans most adult specialties. The CCRU team prioritises patient referrals and provides medical direction for care during transport. It is optimised for immediate resuscitation upon arrival, and institutes prompt collaboration with subspecialty services for rapid intervention when warranted. The CCRU staff also work hand in hand with the staff in downstream definitive treatment locations for the patient (e.g. specialised intensive care units and intermediate care units) to ensure bed availability for the next patient. Previously we have reported that this 6-bed unit, which represents 3.8% of adult critical care beds at UMMC/STC was associated with a 64.5% increase in total critical care transfers, with a 93.6% increase in critically ill surgical patients in its first year of operation. Given this paradigm changing way of how most adult non-trauma critical care transfers come to UMMC, we sought to summarise the CCRU care model and processes to inform other referral centres seeking to improve their capacity and capability to care for critically ill time-sensitive transfers.

In the United States, patients with time-sensitive critical illnesses typically access care at their local hospital's emergency department (ED). Most hospitals are community based, and only a fraction of patients initially present to a tertiary care hospital (American Hospital Association 2017). Patients with critical conditions exceeding the resources of a community hospital require transfer to a higher level of care (Iwashyna et. al 2009; 2012). In addition to the requisite expertise, the accepting facility must have an available bed.

In the U.S., academic medical centres fulfil the role of referral hospital for most communities. These tertiary or quaternary centres generally have a higher proportion of critical care beds, but frequently do not have one immediately available, since they typically have higher occupancy rates (Wunsch et al. 2013). Hence, numerous critically ill patients experience delays to specialised care for time-sensitive conditions (Cardoso et al. 2011).

Similar to other regions, the Delaware, Maryland, District of Columbia (D.C.) and Northern Virginia (DELMARVA) community hospitals have significant challenges when transferring patients. To ensure patients receive timely consultation, quality inter-hospital transfer care, immediate resuscitation and intervention on arrival, the University of Maryland Medical Center/R Adams Cowley Shock Trauma Center (UMMC/STC), created the Critical Care Resuscitation Unit (CCRU). We previously published our initial experience demonstrating decreased time to specialised care and an increase in transfer volume (Scalea et al. 2016). This paper describes the concepts, implementation and operation of the CCRU.

Before the CCRU

In the past decade, UMMC/STC experienced significant expansion of several specialty services, all of which have a component of emergency care: acute care emergency surgery, cardiac surgery with a burgeoning extracorporeal membrane oxygenation (ECMO) programme, stroke service, neurosurgery and vascular surgery. Despite this growth, patients with time-sensitive emergencies frequently could not be transferred due to the lack of an immediately available intensive care unit (ICU) bed. Prior to opening the CCRU, 25% of critically ill patients referred to UMMC/STC could not be transferred. For those who were transferred, the median time from consultation to arrival was almost 4 hours (Scalea et al. 2016). The UMMC campus, which includes UMMC and the R Adams Cowley Shock Trauma Center (STC), has 148 adult ICU beds distributed across seven units and nearly 750 adult licensed beds. While this ratio exceeds the national average of ICU to total hospital beds (19.7% vs 12.4% (Wallace et al. 2015)), it was inadequate to accommodate many critically ill patient transfers.

ICU bed availability was not the only challenge. Coordination of care among subspecialty services and various

Quincy Tran[1,2,4], James OíConnor[1,4], Brooke Andersen[4], Theresa DiNardo[5], Karen Doyle[4], Deborah Stein[1,4], Samuel Tisherman[1,4], Lewis Rubinson[1,4]

Affiliations:
1. University of Maryland School of Medicine, Baltimore, MD
2. Department of Emergency Medicine, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, Baltimore, MD
3. Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Maryland Medical Center, Baltimore, MD
4. Program in Trauma and Trauma Critical Care, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, Baltimore, MD
5. R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, Baltimore, MD

ICUs was problematic. Also, workflow in a traditional ICU, which focuses on longitudinal care, is not ideally suited to manage multiple transfers of critically ill patients.

Lessons from the Maryland Trauma System: conceptual framework for design and implementation of the CCRU

Trauma care requires a comprehensive system, including pre-hospital providers, rapid transport and tiered levels of trauma hospitals, with distinct expertise and resources. For nearly five decades, Maryland made the vision of Dr. R Adams Cowley a reality by incorporating these essential components into a fully integrated, statewide trauma system.

The point of entry to the STC for injured patients, both from the field and transfers from other facilities, is the Trauma Resuscitation Unit (TRU), staffed 24/7 by a comprehensive trauma team led by an attending trauma surgeon. On arrival, the trauma team is already assembled allowing immediate assessment and interventions. The mature UMMC/STC trauma system, which cares for nearly 8,000 patients per year, has succeeded in part because critically injured patients are managed by immediately available, specialty-trained physicians, nurses and allied health professionals. It seemed reasonable to extrapolate this model of care delivery for non-traumatic, critically ill patients with time-sensitive conditions (Kahn et al. 2008).

CCRU model: multi-specialty resuscitation unit

More than one quarter of patients admitted to UMMC/STC are transferred from DELMARVA hospitals. Early in the conceptual phase focused on improving the transfer process, the question of who required urgent or emergent transfer was considered. Numerous studies have demonstrated that high-volume centres have improved outcomes for a wide range of surgical diseases, including complex gastrointestinal surgery (Gordon et al. 1999; 1995), craniotomies (Long et al. 2011) and cardiothoracic procedures (Finks et al. 2011; Cheung et

Table 1. Volume-sensitive diseases and effects on outcomes

Patient population	Volume	Outcome
Mechanically ventilated patients	>400 per year	25.5% in-hospital mortality (Kahn et al. 2006)
	<150 per year	34.2 in-hospital mortality
ICU pneumonia	37-117 cases treated	14.3% mortality (Lin et al. 2008)
	118-314 cases treated	11.4% mortality
	>315 cases treated	8.1% mortality
Craniotomy	> 50 per year	2.5% in-hospital mortality (Long et al. 2003)
	< 50 per year	4.9% in-hospital mortality
Oesophagectomy	Very high volume	8.4% mortality (Birkmeyer et al. 2002)
	Very low volume	20.3% mortality
Pancreatectomy	Very high volume	3.8% mortality (Birkmeyer et al. 2002)
	Very low volume	16.3% mortality

Table 2. Time-sensitive diseases and effects of interventions

Type of disease	Outcome	Intervention
Aortic dissection, type A	Mortality 1% per hour	Not undergoing surgical intervention (Hagan et al. 2006)
Ruptured abdominal aortic aneurysm	Overall mortality rate 81% (Reimerink et al. 2013)	
	Mortality 40%	Intervention was delayed more than 45 minutes (Zdanowski et al. 2002)
Spontaneous intracerebral haemorrhage for patients with GCS > 8	12-month GOS > 3 = 33%	Operative treatment within 6-8 hours (Pantazis et al. 2006)
	12-month GOS > 3 = 9%	Medical management
Ischaemic stroke patients receiving tPA	72-hour neurologic improvement = 80% of patients	Endovascular therapy at less than 210 minutes from symptom Onset (Campbell et al. 2015)
	90-day modified Rankin Scale 0-2: 71%	
	72-hour neurologic improvement = 37%	Medical treatment
	90-day modified Rankin Scale 0-2: 40%	
Massive pulmonary embolism	Mortality 3.6%	Surgical embolectomy (Aymard et al. 2013)
	Mortality 13.5%	Thrombolysis

al. 2009). An increasing amount of data demonstrates this effect is not exclusive to surgery (**Table 1**).

Patients cared for at centres specialising in acute stroke, acute coronary syndrome and cardiac arrest have shown improved outcomes (Campbell et al. 2015; Edwards and Carr 2010; Elmer et al. 2016; Spaite et al. 2014). This holds true for other serious conditions: subarachnoid haemorrhage (Berman et al. 2003), profound respiratory failure requiring mechanical ventilation (Lin et al. 2008; Peek et al. 2009), and severe sepsis (Peelen et al. 2007; Ofoma et al. 2017). A recent systematic review examining a wide range of critical illnesses reported that critically ill patients uniformly had improved outcomes at a high-volume, regionalised centre (Nguyen et al. 2015). In addition to volume-dependent disease outcomes, there are time-sensitive conditions for which the appropriate therapy is only available at select hospitals (e.g. type A aortic dissection, acute stroke amenable to clot retrieval (**Table 2**)).

"designed to provide comprehensive critical care, not simply a landing zone for patients awaiting a destination icu"

For some emergency conditions (e.g. massive pulmonary embolism, severe pancreatitis, sepsis), the majority of patients arrive via inter-hospital transfers. Our analysis suggested a broad range of critically ill patients across numerous specialties would benefit from expeditious transfer to our facility. Since the impediment to transfer was frequently the lack of an available specialty ICU bed, we considered increasing bed capacity in some or all of the ICUs. We recognised that transfer requests are not uniformly distributed across time and would require maintaining an available ICU bed in each specialty unit. This was neither economically nor logistically feasible. Another option we considered was increasing ICU bed capacity only in select units. While this would increase transfer volume, the result would be patients boarding in a different subspecialty ICU. This may be detrimental, as several studies suggest that outcomes are worse when care is delivered in another specialty ICU (Mirski et al. 2001; Pascual et al. 2014). These challenges were the impetus to develop the CCRU: a multidisciplinary ICU that manages the spectrum of adults transferred with time-sensitive, critical illness. The CCRU was conceived as a "short-stay" unit, with the goal length of stay 6 to 12 hours. It would admit, resuscitate and stabilise patients, who eventually would be transferred to the operating room or appropriate specialty ICU, once a bed became available. Opened in July 2013, the CCRU is a 6-bed unit with 24-hour intensivist coverage.

One of the lessons learned from the trauma model was the importance of immediate expert intervention as soon as the patient arrives. Therefore the CCRU was designed to provide comprehensive critical care, not simply a landing zone for patients awaiting a destination ICU. This necessitated an extremely broad scope of practice. In order to provide regional access for critically ill patient transfers, we needed the unit to have the personnel, equipment and systems to manage a spectrum of adult, non-traumatic critical illness.

A single unified ICU providing comprehensive critical care must be staffed with providers capable of working across the breadth of specialties. Prior to opening the CCRU we identified a cadre of ICU nurses with extensive and diverse critical care experience. Physician leadership and nurse educators implemented a rigorous and compressive training programme enabling the staff to be trained in all aspects of critical care. Unlike most critical care nurses with a depth of expertise within a focused specialty, the CCRU staff needed expertise across many specialties without compromising the knowledge inherent with subspecialisation.

The CCRU intensivist must also have expertise in rapid evaluation and resuscitation for all forms of critical diseases and be able to closely collaborate with various subspecialists. We determined that emergency medicine physicians with critical care fellowship training were ideally suited; they comprise the vast majority of the attending staff. The remainder are fellowship-trained medical and surgical intensivists with significant experience in both medical and surgical ICUs.

The intensivists work closely with the CCRU advanced practice providers (APPs), who are carefully selected based on extensive experience in an array of critical care settings or formal fellowship training. They complete a three- to six-month orientation, including procedural simulation and skills labs. The APP works in tandem with the intensivist to manage resuscitations and coordinated care, allowing the physician to manage institutional and unit flow.

CCRU process overview: coordination and communication from the time of consult to definitive care

Pre-arrival coordination

A formalised transfer system is essential to coordinate referrals and prioritise transfers by illness severity and time sensitivity. Additionally, it must provide medical direction during transport. When a hospital requests a transfer to UMMC/STC, they contact the central transfer centre, Maryland Express Care (MEC), which coordinates approximately 11,000 transfers annually. MEC facilitates consultation between outside providers, CCRU and accepting services at UMMC/STC, provides ground transportation and coordinates aeromedical transport.

Prior to the CCRU, communication regarding transfer of critically ill patients between the accepting subspecialty and critical care services was informal and frequently limited. To improve this process, phone requests to MEC for transfer now include the referring

physician, CCRU intensivist and the appropriate UMMC specialty attending. The CCRU intensivist prioritises transfers, determines the appropriate mode of transportation and provides medical oversight during transport.

MEC arranges the transport team, including at least one critical care nurse and one technologist with emergency medical team (EMT)-paramedic certification. For patients transferred for refractory respiratory failure and possible ECMO, a respiratory therapist is added to the team. When the team arrives at the referring hospital they contact the CCRU attending, provide updated information and receive medical direction when warranted.

Anticipatory posture

In order to reduce time to intervention once the patient arrives, the CCRU engages in "anticipatory posture", a concept used in military and political theory, which constitutes setting up for active engagement and pre-empting what is required to best address the situation before it presents itself (Larsen 2013). In this context, the CCRU team uses data from the initial consult, a standardised nurse report form (provided from referring nurse to CCRU nursing staff), the transport team's update, and the statewide health information exchange (Chesapeake Regional Information System 2017) to prepare infusions, pre-position equipment and anticipate likely procedural interventions. These include bedside decompressive laparotomy, ECMO cannulation, resuscitative endovascular balloon occlusion of the aorta (REBOA) insertion, oesophageal-gastric balloon device placement, endobronchial interventions, renal replacement therapy and apheresis as indicated. This process limits delays to critical interventions and reduces the organisational chaos associated with attempting to rapidly gather staff and equipment from multiple locations.

Attention to flow

By design, ICU workflows are structured to deliver longitudinal care rather than optimising care for the next admission. An unstable patient or several simultaneous admissions often disrupts this workflow. Conversely, the CCRU workflow focuses primarily on patient admission, resuscitation, stabilisation and disposition. The CCRU is a mixed model unit, incorporating the benefits of an ED as an access point centred on triage and flow, while concurrently delivering comprehensive multi-specialty critical care. Unlike many EDs, the providers can focus on the critically ill and are not distracted by myriad non-acute patients. Additionally, since specialists are involved in the initial consultation and decision to transfer the patient, there is no delay in specialty-driven care that occasionally occurs in the ED.

The CCRU is designed as a short-stay unit. Patients rarely require extended ICU care. However, if they do there are daily rounds as in any ICU, but rounds occur between new admissions. This workflow allows the CCRU team to maintain an anticipatory posture for the next critically ill patient transfer. This requires the CCRU attending and charge nurse to be in frequent communication with UMMC ICUs, procedural suites, operating rooms and the patient placement centre to facilitate disposition of CCRU patients.

Towards a culture of safely saying yes

We incorporated checks and balances to achieve defined goals in a safe, effective manner that consistently yields improved outcomes. Several key components are described below.

Requirement-based unit

Rather than fitting care into existing hospital systems, we created new systems based on the specific requirements of rapid diagnosis and emergent resuscitation. Unit design, processes and staffing models were developed to meet these requirements.

Optimising time to interventions

We developed guidelines which foster rapid treatment and mitigate existing barriers to care delivery. Examples include implementing a system providing emergency medications and infusions available prior to the patient's arrival or registration within the hospital's electronic medical record, as well as maintaining uncross-matched blood in the CCRU.

All cases are discussed directly with fellows or attending physicians. This allows junior trainees to be active learners without introducing treatment delays intrinsic to the traditional medical hierarchy. Additionally, the CCRU APPs provide continuity in this high-volume, high-acuity unit that may be challenging to accomplish in an academic model with rotating residents.

Quality assurance

To deliver care which is equivalent to that provided in UMMC specialty ICUs, the CCRU maintains a robust, non-punitive quality assurance system. We foster a culture among providers and staff to strive for constant improvement. Adverse events and opportunities for process improvement are documented daily by the charge nurse. When an area for improvement is identified, a system-level change is implemented and tracked to ensure the desired result is obtained.

Standardised, streamlined communication

Since medical errors are associated with transitions of care (Horwitz et al. 2008), handoffs inherent in this model require a deliberate and standardised communication process. Detailed clinical information, including imaging, is obtained from the referring hospital; transport oversight and anticipatory posture are standard practice. At change of shift there is a face-to-face, detailed handoff between physicians, advanced practice providers and nurses.

Protocols and checklists

We created protocols, guidelines and checklists for high-risk procedures performed in the CCRU. Infrequently, a high-consequence emergency procedure (e.g. Minnesota tube, transvenous pacemaker, surgical airway, ECMO cannulation) is indicated and must be promptly and competently performed. Having immediately available guidelines and checklists minimises errors that may occur with these procedures.

Emergency inpatient rescue

With an almost omnipresent open bed, the CCRU is able to admit and stabilise decompensating UMMC/STC inpatients when no ICU bed is available (Jones et al. 2016). Rapid response personnel can quickly transport decompensating patients to the CCRU rather than continue resuscitation in a suboptimal, resource-limited environment. The CCRU can also decompress UMMC ED by admitting and managing

critically ill patients awaiting an ICU bed, which has been shown to decrease mortality (Chaflin et al. 2007).

Limitations of model and areas for growth

While referrals to high-volume centres have been shown to be effective for many conditions, regionalisation has yet to demonstrate improved outcomes for all critical diseases. Studies have questioned transferring septic patients in rural settings (Mohr et al. 2016), and data are mixed on patients with ruptured abdominal aortic aneurysms (Mell et al. 2014). However, this may reflect delays in timely transfer and other logistical impediments. It is possible that an integrated, coordinated transfer system could mitigate these limitations, leading to improved outcomes. Clearly, further system development and evaluation are required.

Although some data demonstrate adverse outcomes for patients boarding in different subspecialty ICUs, it remains to be determined whether the CCRU model avoids this problem. That is another area that warrants future study.

To ensure an ICU bed is available, downstream flow must be a priority. Increasing overall admissions requires the receiving hospital must optimise patient throughput, including timely discharges.

Future directions and next steps

Currently, admissions to each subspecialty ICU are determined by the individual responsible for unit triage. We envision improved access and flow by having a single intensivist, with broad critical care experience, direct the ICU admission of all critically ill patients. Ideally, they would direct traffic across all ICUs within a regionalised system.

Although the CCRU has increased access to specialty care and transfers of critically ill patients, as well as decreased transport times (Scalea et al. 2016), prospective data collection is essential to fully understand the impact on patient outcomes. Additionally, the CCRU was created to address the needs specific at UMMC/STC and may be applicable to other institutions, but that remains to be determined. The CCRU is a template for delivering care to critically ill patients requiring transfer to a tertiary or quaternary centre. Others may adopt or modify the CCRU model to suit their particular institutional needs.

Conclusion

The CCRU has increased transfer volume and decreased time to definitive, specialty care for critically ill patients with time-sensitive conditions. This innovative unit ensures rapid access, medical control during transport, close coordination with specialty services and enhanced throughput. With a highly trained, dedicated staff focused on critically ill transfers, expeditious evaluation, appropriate interventions and close coordination with specialty services, the CCRU is a paradigm shift in care delivery. ■

Conflicts of interest and sources of funding

The authors have none to report.

Abbreviations

APP advanced practice providers

CCRU Critical Care Resuscitation Unit

DELMARVA Delaware, Maryland, District of Columbia (D.C.) and Northern Virginia

ECMO extracorporeal membrane oxygenation

ED emergency department

EMT emergency medical team

ICU intensive care unit

MEC Maryland Express Care

UMMC/STC University of Maryland Medical Center/ R Adams Cowley Shock Trauma Center

STCR Adams Cowley Shock Trauma Center

TRU Trauma Resuscitation Unit

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CRITICAL CARE SYMPOSIUM

Variation in end-of-life care

Do we need yet another standard operating procedure?

Variability in end-of-life care would seem to demand a standard operating procedure, but a roadmap towards harmonisation arguably would be easier to implement.

Andrej Michalsen
Consultant
Department of Anaesthesiology and Critical Care Medicine
Tettnang Hospital
Tettnang, Germany

andrejmichalsen@hotmail.de

Mainly due to enormous pharmacological and technological innovation during the last decades, intensive care medicine can help patients survive, whose vital functions are seriously compromised or have failed temporarily. However, still approximately 15 to 30% of patients treated in intensive care units (ICUs) succumb to their illnesses or injuries (Vincent et al. 2014; Moran et al. 2008). The majority of these patients die after limitations of treatment were implemented, that is after the treatment goal was altered from cure to comfort. In most cases, life-sustaining treatments are withheld or withdrawn, and the emphasis of the therapy towards the end of the patients' lives rests on alleviating their suffering and creating an atmosphere of dignity, comfort, and peace (Curtis and Rubenfeld 2001).

The care at the end of patients' lives—"end-of-life care" (EOLC)—has evolved into an important tool within the armamentarium of the modern critical care specialist, aided by palliative care specialists, if required and feasible (Baker et al. 2015; Aslakson et al. 2014). Despite widespread agreement as to the general need for adequate EOLC, there is considerable variation regarding its practice and implementation—not only between continents or countries, but also within countries, regions and even hospitals (Myburgh et al. 2016; Mark et al. 2015; Sprung et al. 2014; Barnato et al. 2012). Arguably, the main proportion of the variation is attributable to the individual providers, the reasons being, amongst others, schools of medical thinking, differences as to prognostication, hierarchy, ignorance, cultural norms, religion and religiosity.

The issue to be discussed henceforth is: How much variability in EOLC should we accept or do we need a clear-cut standard operating procedure (SOP) on the matter?

Standard operating procedures are written instructions that aim to assist clinicians in making decisions about routine procedures and treatments for specific conditions in specific locations. They are linked to evidence and are meant to facilitate good clinical practice (Davies 2009). By definition and goal, a SOP is quite similar to a guideline (oit.va.gov/services/TRM/TRMGlossaryPage.aspx), perhaps a little more circumscribed.

In healthcare, SOPs or guidelines have been widely developed and implemented, especially for scenarios where time-critical decisions need to be taken, often with scarce information about the patients, with various disciplines and professions involved, and with a requirement for noticeable leadership. Prominent examples for such scenarios are cardiopulmonary resuscitation, (prehospital) airway management, management of myocardial infarction, and (initial) sepsis treatment. Although few would argue with the benefits of guidelines in these circumstances, physicians' adherence to them could be pointedly described as patchy at times (Milonas et al. 2017; UK National Surgical Research Collaborative 2017).

Whilst decisions regarding EOLC require prudent leadership as well, the decision-making process might appear to differ from the scenarios mentioned above:

- In EOLC, decisions regarding complex medical situations and/or a change of the goal of treatment need to be taken through interprofessional shared decision-making (IP-SDM). This denotes a collaborative process amongst healthcare providers that allows for jointly reached decisions regarding important treatment questions and taking into account the best scientific evidence available and the combined expertise of all involved. Although IP-SDM is about decision-making within the treating healthcare team, the patient's values, goals and preferences, as far as they are known, should of course be included in the decision-making process.
- In EOLC, important treatment decisions require the patient or his/her legal representative to be part of the shared decision-making process (Kon et al. 2016). Therefore, such decisions cannot be taken unless adequate information about the respective patient has been gathered, especially regarding his/her values, goals and preferences—perhaps with the rare exception that neither the patient nor anyone else can provide the healthcare team with any information on these issues.
- In EOLC, decisions should not be time-critical. To the contrary, the decision-making process requires, amongst others, an adequate setting, a patient-team relationship of mutual trust, if ever possible, and sufficient openness to deliberate upon the best treatment plan for the individual patient under the given circumstances. The respective family conferences may require time and, especially, time to listen and appreciate the person behind the patient; the VALUE template of Curtis and White has been recommended in that regard (Curtis and White 2008).

The quintessence of EOLC is to align the medically indicated treatment option(s) with the wishes and goals of each individual patient under the specific circumstances, i.e. to align instrumental and value rationality as best as possible (**Figure**) (Neitzke et al. 2016).

In practice, this task often comprises, but is not limited to, reaching a joint decision amongst the treating team as well as a shared decision with the patient and/or his/her legal representative regarding the extent of treatment and the (change of) treatment goals as well as the subsequent implementation of adequate symptom control, both physically and mentally (Michalsen and Hartog 2013).

"a roadmap is proposed to harmonise end-of-life care"

This task apparently has not become simpler over the last years, mainly because on the one hand technological innovations have offered impressive advanced treatment options, also within ageing societies, and many patients have increased their expectations and demands on healthcare systems worldwide. On the other hand, many contemporaries fear to fall victim to the broad mechanisation of health care and its soulless delivery to them. The fundamental issue of prognostication requires transparency and the admission of uncertainty from the healthcare team, whilst patients and families would hope for an early and accurate prognosis as to the immediate and long-term outcomes (Neitzke et al. 2016; Ridley and Fisher 2013). Finally, an increasing concern regarding EOLC pertains to what is called "cultural relativism" (Beck 2015).

People do things differently; they value different things, believe in different authorities, follow different customs, but most importantly differ on what things they count as right or wrong, permissible or impermissible—also regarding healthcare. Such differences and the disagreements they precipitate can be addressed in more than one way, depending on one's cultural, religious and social background, often without reaching common ground. How can we judge the ways of others and assume that we hold the only right answer? In modern societies, it is no longer obvious that the views of the professionals are leading the way, yet medical care should not abandon ethical core values—and cannot circumvent the respective legal stipulations.

Would then an SOP be needed to decrease the variability in EOLC? Arguably, the question should rather read, would an SOP be helpful and enforceable?

Given the complexities of EOLC outlined briefly above, an SOP would either have to be very broad to gain wide acceptance, thereby neglecting special regional and local circumstances, or it would have to be specifically orientated towards certain healthcare settings, thereby losing worldwide applicability. Even though there appears to be worldwide professional consensus on certain principles in EOLC (Sprung et al. 2014), it remains unclear whether they are implemented into daily practice outside the "circles of forerunners". Furthermore, imagine a simple SOP for EOLC as succinct as the algorithm for basic life support: perhaps easy to follow, but missing the mission.

Instead of yet another SOP, adequate EOLC requires a dedicated healthcare team, truthful communication and cooperation within the team, understanding of the patient's wishes, values and goals, assessment of the medical option(s) and their indications for the individual patient, shared decision-making with the patient and his/her family, and, not least, an ethical climate within the ICU to allow for adequate deliberation and discussion without hierarchical or economic pressure.

Therefore, a roadmap rather than an SOP is proposed (**Table**) to harmonise EOLC across institutions and, perhaps, healthcare systems. ■

Figure. Aligning instrumental and value rationality in end-of-life care.

1. The medical team decides on medical matters, especially whether a certain treatment is or is not (or no longer) indicated to reach a medical goal (instrumental rationality).
2. The patient decides on the shaping of his/her life, especially whether he/she consents to the process of reaching the designated medical goal and the expected quality of life thereafter (value rationality).

Table. Roadmap to harmonise end-of-life care

1. Determine attainable medical treatment goals and remain open to potential changes thereof.
2. Elucidate the patient's goals, values, wishes
3. Reach a joint decision concerning the extent and potential limits of treatment -both within the team and with the patient/the family.
4. Know how to implement limitations of therapy.
5. Manage possible confilcts with a fair and transparent process

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"Simulate, or not to simulate?"

Evolution in medicine and the anaesthesia context

A brief discussion about the importance and the state of the art of simulation in anaesthesia and intensive care medicine.

Miriam Poggioli
Department of Translational Medicine, School of Specialisation in Intensive Care Anaesthesia and Pain
University of Eastern Piedmont

poggioli.miriam@gmail.com

Valentina Rondi
Department of Translational Medicine, School of Specialisation in Intensive Care Anaesthesia and Pain
University of Eastern Piedmont

valerondi88@gmail.com

Training in simulation plays a key role in complex systems such as aviation and the nuclear industry, to investigate predictable errors that lead to adverse outcomes. The advancement made by aviation integrating simulation in training over the past years is relevant, whereas in medicine simulation remains marginal, but is now rising in use. In medicine we are asking if simulation really works and if there is a place for it in medical training. Perhaps the answer is yes.

In the last few years, the use of mannequin-based simulation has become a mainstay in physician education in particular through the Basic Life Support (BLS), the Advanced Life Support (ALS) or the Advanced Trauma Life Support (ATLS) (Miyasaka et al. 2015). The American College of Critical Care Medicine recommended the use of simulation to enhance resident training in critical care (Dorman et al. 2004). Furthermore, the Institute of Medicine report *To Err is Human* suggested simulation training to reduce preventable errors (Kohn et al. 2000).

In the USA about 98,000 deaths per year are due to medical errors, more than vehicle accidents, cancer or AIDS (Kohn et al. 2000). In Canada, around 7.5% of hospital admissions will result in an adverse event (Naik and Brien 2013).

So, what is our answer to this evidence?

Can we be sure that we are educating students and trainees in the most effective way possible? On the contrary, Dudeck et al. affirmed that our programmes are not always able to identify underperforming residents and that the lack of evaluating documentation leads to undefined level of competence. Too often, current trainees are assessed using poorly and non-standardised metrics (Levine and Shorten 2016; Dudeck et al. 2015).

Educational programmes

Strong evidence supports the importance of increasing physicians and healthcare professional's competencies with a broader set to improve the healthcare system (Naik and Brien 2013). For this reason, many countries developed a lot of projects aimed at creating simulation-based assessment including essential skills, technical and non-technical, for the practitioner.

"simulation scenarios allow learners deliberate practice of crisis management with no risk for patient safety or quality of care"

In the literature, many articles have tried to develop, implement and evaluate a set of consensus-driven standardised simulation scenarios (mannequin-based) that each trainee must complete satisfactorily prior to completion of certification for anaesthesiology residents (Chiu et al. 2016), paediatric residents (Mitzman et al. 2017; Bank et al. 2015), obstetrics and gynaecology residents, management of trauma and surgical critical care patients (Miyasaka et al. 2015). The authors describe methods to achieve competencies that should be included in the educational programmes. They usually employ the Delphi Method through a task force of experts. None of the papers go into detail about the contents selected or include the simulation scenarios list chosen for each subject, however.

This kind of training refers to Miller's pyramid competence, which sustains the progression from "knows" and "knows how" to "shows how" and "does" (Jonker et al. 2017). Simulation scenarios allow learners deliberate practice of crisis management with no risk for patient safety or quality of care, and if designed for evaluation, permit the "shows how" level of assessment (Jonker et al. 2017).

Simulation in anaesthesia

Training in simulation fits well with the resident's educational path in anaesthesia and intensive care. In Europe there is a wide variability of training programmes in different countries. In 2012, the Union of European Medical Specialists issued the latest revision of their guidelines on Training Requirements for the Specialty of Anaesthesia, Pain and Intensive Care Medicine. These guidelines aim to harmonise postgraduate educational courses to facilitate transfer of anaesthetists across Europe (Espey et al. 2017).

Through an online survey, Jonker et al. (2017) collected a description of European training programmes in three types of board:

- Knowledge-based (with final exam oral or written),
- Knowledge- and skills-based (with a specified number of procedures evidenced by a logbook),
- Competency-based (with workplace assessment).

Many countries are now evolving towards a competency-based approach to training, using a larger

Pier Luigi Ingrassia
Researcher
Interdepartmental Centre of Innovative Teaching and Simulation in Medicine and Healthcare (SIMNOVA)
University of Eastern Piedmont

pierluigi.ingrassia@med.uniupo.it

Simone Bazurro
Department of Integrated Surgical and Diagnostic Sciences, Anaesthesia and Intensive Care
The IRCCS Polyclinic Hospital San Martino
University of Genoa
Italy

simonebazurro@gmail.com

Iole Brunetti
Anaesthesia and Intensive Care
The IRCCS Polyclinic Hospital San Martino
Genoa
Italy

brunettimed@gmail.com

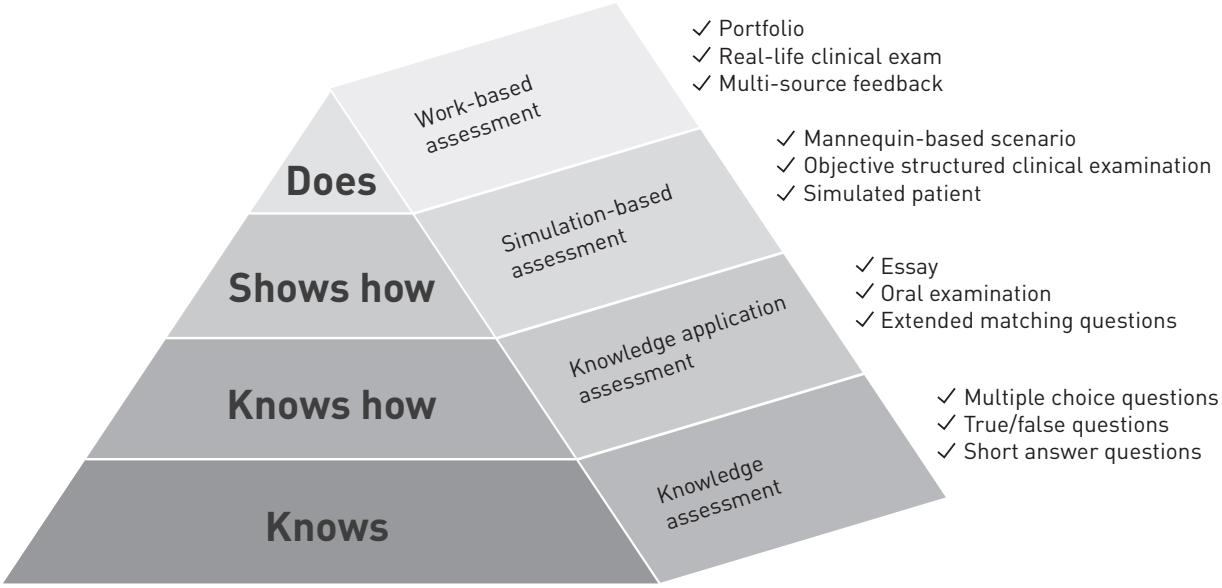
number of assessment tools to support trainees' competence. Establishing learning outcomes that can be assessed to guarantee a required level of competence of all European anaesthetists demands ongoing effort. In this optic, the future role of simulation in anaesthesia will increase. In one study, a simulation-based curriculum improved performance scores in management of medical emergencies and should be incorporated into residency education (Barra et al. 2018). Training for novice residents through simulation courses is effective and safe to rapidly acquire and develop basic skills specific to anaesthesiology (Barsuk et al. 2009a).

Technical and non-technical skills in anaesthesia

The literature supports the use of simulation to educate and improve technical skills (TS) and non-technical skills (NTS): Naik and Brien (2013) define TS such as medical knowledge and procedural ability mapped to a larger group of competencies; NTS are identified as task management, teamwork, leadership, situational awareness and decision-making.

Technology is a crucial tool supporting development, teaching and achievement of practical abilities in safe environments. It allows participants to try and to make mistakes without discomfort or risks for patients.

In the anaesthesia context a simulation-based education is useful in procedures to reduce adverse outcomes and technical error and to shorten learning curves, i.e. catheter bloodstream infection (Barsuk et al. 2009a), central venous catheter placement (Barsuk et al. 2009b), lumbar puncture skill (Barsuk et al. 2012), ultrasound use in loco-regional anaesthesia (De Oliveira Filho et al. 2017), endotracheal intubation (Howells et al. 1973) and airway management in general (Stringer et al. 2002; Cumin and Merry 2007).



Source: Miller (1990)

Instead, NTS are more difficult to practise and evaluate. Probably more time is required to develop programmes to train and to expand these skills, aware of their contribution to system errors, morbidity and mortality. It is estimated that about 70-80% of medical errors are attributable to failing in these contexts (Flin et al. 2017). Without balanced curriculum design, the challenge in teaching NTS for patient safety can result in their overall marginalisation (Naik and Brien 2013).

Human behaviour is a variable that can influence task execution and it plays a crucial role in the anaesthesia context in relation to NTS. These types of competences can be described as crew resource management or crisis resource management (CRM) (Flin and Maran 2015).

Anaesthesiologists do not typically receive training in CRM, although they are called upon to manage life-threatening crises at a moment's notice. A recent paper demonstrated that CRM training for team leaders only is more effective than mere clinical training of team members (Castealo et al. 2015).

Over the last decade, the description of NTS with taxonomies has allowed the identification of essential skills for anaesthetic practitioners:

1. situation awareness, monitoring of the task and noticing changes in the environment
2. decision-making, reaching a judgment, selecting an option and choosing the action to do

3. teamwork, maintenance of team harmony, colleagues' motivation and coordination using both verbal and non-verbal communication
4. leadership, managing personnel and material resources
5. coping with stress
6. managing fatigue.

In order to develop these tasks through simulation-based training programmes, scenarios and debriefing of scenarios allow participants to identify and analyse effective and less effective behaviours that impact on patients' outcomes. It is clear that, for simulation, both quality and frequency of experience are important in terms of impact on clinical practice and patient's safety: they must be considered and determined.

"it remains uncertain how to measure the real transfer of simulation training into clinical practice"

In recent years, the American Society of Anesthesiology decided to integrate simulation-based training with Maintenance of Certification in Anesthesiology (MOCA) (Steadman and Huang 2012). High-fidelity simulation increased retention of skills and so improved learner outcomes. As healthcare professionals, we must be ready to demonstrate our skills and the maintenance of proficiency. To do this in the best way possible training and re-training in simulation should be a useful opportunity (Krage and Erwteman 2015) .

It remains uncertain how to measure the real transfer of simulation training into clinical practice. So, more research studies are needed in the future to establish the improvement in terms of clinical performance, patient outcome and maintenance of competences. Our hope is that each nation will implement and integrate training programmes with a simulation-based curriculum, in order to standardise curricula and the approach to clinical practice respecting different features and characteristics. Ordinary use of simulation may prepare our next generation of medical educators. ■

Conflict of interest

None declared.

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Being an expert witness

Describes the practicalities of being an expert witness and explains what qualities are necessary to succeed in this important role.

John Dale-Skinner
Senior medical claims handler
Medical Defence Union
London, UK

media@themdu.com

@the_mdu

Our legal system couldn't function without medical expert witnesses. From personal injury claims to criminal prosecutions, there is a constant demand for experienced doctors with the necessary skills and authority to take on this role. But while expert witness work can be intensely rewarding it also requires long-term commitment, integrity and a willingness to stand up in court.

The importance of expert evidence

A widespread misconception about expert witnesses is that they give evidence on behalf of one of the parties in a court case. However, the actual purpose of an expert is to assist a court or tribunal by giving an *impartial opinion* on the facts, in the form of a written report or in oral evidence which can be understood by the court and parties involved.

An expert's report can also influence case management at an earlier stage in proceedings. In clinical negligence cases, for example, expert reports are exchanged between the claimant and the defendant(s). Experts also meet to prepare a joint statement which helps narrow down the issues, saving time and costs. This is why the majority of clinical negligence claims discontinue or settle before reaching the trial stage.

The role of an expert

Unlike a witness of fact (also known as a professional witness) who is called to testify about their own contact with a patient, an expert witness will not have had any involvement in the case until they are instructed. They are also free to decide whether or not to act in a case and can charge a fee.

After accepting instructions in a case, an expert is required to formulate an opinion based on their clinical examination of the patient (in some cases), a review of the records and other documentation and (usually) a search of the relevant literature including guidelines, peer-reviewed journals or textbooks.

> "while expert witness work can be intensely rewarding it also requires long-term commitment, integrity and a willingness to stand up in court"

Instructed experts must then produce an expert report which responds to the questions raised in their instructions. Expert reports should reference all the information that has been used to form an opinion and if appropriate any literature that would support a different opinion, explaining why the expert's interpretation leads them to a particular conclusion. If there is not enough information to reach a conclusion on a particular point, this must be made clear. Equally, the expert can also include comments that go beyond the scope of their original instructions, provided it is within their area of expertise. At the end of the report, the expert must sign a declaration confirming that they understand their duty to the court and that they have complied with that duty.

However, submitting their report is only the first stage in an expert's involvement in a case. They may need to take part in case conferences with lawyers and other interested parties, and ultimately they must be available to attend court and give evidence. A court appearance requires experts to be familiar with all the evidence relied upon by the judge. This includes their own report and also reports from the other expert witnesses. They must be able to answer, competently and credibly, the other party's questions during cross-examination—the best experts on the stand are those who are able to provide a well-reasoned opinion, having already considered alternative views.

Ethical and legal duties

The General Medical Council (GMC) publication *Acting as a witness in legal proceedings* (GMC 2013) sets out guidance for witnesses, expanding on the core principles set out in *Good medical practice* (GMC 2013) These can be summarised as:

- Be impartial—your duty is to the court not the person who instructs or pays you
- Confine statements to areas of relevant knowledge or direct experience
- Declare conflicts of interest without delay
- Do not disclose confidential information without consent (other than to parties in the proceedings, or where obliged by law or ordered by the court)
- Inform the appropriate people if you change your view on a material matter
- Ensure that instructions you are given are clear and unambiguous

As well as the GMC's guidance, expert witnesses must also comply with their legal obligations. For example, an

expert witness acting in a claim must be familiar with Part 35 of the Civil Procedure Rules, which governs expert evidence and the Civil Justice Protocol for the instruction of experts.

Risks and liability

Working as an expert witness does carry some medico-legal risks and it is therefore essential that experts are adequately indemnified for their medico-legal work. The Medical Defence Union (MDU) advises its members to keep us updated of their working circumstances.

Experts can face GMC investigations and in extreme cases could be sued for negligence or breach of contract. This followed a landmark Supreme Court ruling in 2011, which ended the right to immunity for expert witnesses.

> "working as an expert witness does carry some medico-legal risks and it is therefore essential that experts are adequately indemnified"

Courts also take a rigorous approach to ensuring that their timetables are met. They may exclude any party from calling expert evidence if the expert reports have not been served on time. If the expert is considered to be at fault, they can be sued or reported to the GMC. Similarly, if a judge criticises an expert for failing to comply with the timetable, there is a risk that they may be found personally liable for all costs.

Avoiding the pitfalls

Here are some useful points to consider, based on the MDU experience of instructing experts and advising doctors in expert witness matters:

- Before accepting instructions, check the names of all those involved in a case, including the solicitor, to ensure there is no conflict of interest. If you have accepted instructions from the other party or have a professional relationship with a clinician who is involved in the case for instance, you may have to decline the case.
- Stick to your own area of expertise. Let the instructing solicitor know if you believe an alternative opinion is necessary.
- Tell the instructing solicitor if you change your opinion as the case progresses and more evidence becomes available. Date any supplementary opinion that you provide.
- Be realistic about the amount of medico-legal work that you can take on, bearing in mind other commitments.
- Inform the instructing solicitor at the outset if there is a chance you won't be able to commit to the entire process e.g. you are planning to retire or travel.
- Ask the instructing solicitor to provide details of the court timetable at the first opportunity and note relevant dates so there is less chance they will be overlooked.
- Ensure you are appropriately indemnified for expert witness work by your medical defence organisation.

Becoming an expert witness

If you have at least 10-15 years' experience in ICU or another area of medicine and think you have what it takes to be an expert witness, you may find it helpful to attend a specialist training course. These often cover important aspects of the role including report writing, the legal process generally and court appearances. It's also a good idea to compile a CV detailing relevant general and specific medical experience, including any teaching posts, publications and lectureships.

To find work as an expert witness, consider registering with an agency or a body like the Expert Witness Institute, which produce directories of experts in the UK. These provide details of the expert and how they can be contacted and may list any high-profile cases in which they have been involved. ■

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Establishing a relationship of trust and care

The role of the chaplain in the ICU

The chaplain is a resource of ethically competent support and a compassionate caring presence for patients, families and ICU staff.

Karen Jones
Director, Pastoral Care and Education
Winthrop-University Hospital
Mineola, NY
USA

KJones@nyuwinthrop.org

An admission to the intensive care unit (ICU) is often a traumatic experience for both patients and families. Although members of the critical care team are specially trained to provide care and treatment requiring close, constant observation, the environment can be overwhelming with machines, tubes, and equipment used in the care of the patient. With what feels like a barrage of requests for information about the patient's medical history, advance care directives and goals of care, families are often challenged to focus on the goal of the healthcare team to help their seriously ill loved one heal and recover. Within the environment of sophisticated diagnostic and therapeutic care in almost every specialty and subspecialty of medicine and surgery, the salient role of the chaplain in the ICU is to be a resource of ethically competent support and a compassionate caring presence for patients, families and the ICU staff. The quality of chaplaincy care is determined by the ethically-competent and compassionate caring connections that are made with patients, families and staff throughout the hospitalisation.

For many patients and families, the ICU admission may elicit fear, frustration, anxiety, and sometimes anger, which are common signs of emotional and spiritual distress.

Addressing spirituality is invaluable to patients and families with severe illness. The spiritual beliefs of patients and their family members are known to influence ethical decision-making about goals of care and end-of-life choices.

Cheryl Palmer, manager of spiritual care services at Barnes Jewish Hospital in St. Louis, Missouri, expresses how important it is to provide spiritual services to the ICU staff:

Working in a hospital is difficult because it means watching people suffer and sometimes die, and then observing the emotional family dynamics that result. It all takes a toll on the staff. Medicine is very demanding, and it does not matter what your job is, everyone feels the intensity in a hospital.

Compassionate care for all

Challenges to providing optimal spiritual care in the ICU centre around education and communication. According to William Nelson, PhD, Director of the Rural Ethics Initiatives at the Dartmouth Initiative for Health Policy and Clinical Practice at Lebanon, New Hampshire:

Clinicians sometimes misunderstand the chaplain's role. Some healthcare workers think the chaplain is trying to impose or only attend to religious beliefs.

The reality is that the chaplain is a trained professional with specialised education and training in mobilising spiritual resources so that patients are enabled to cope more effectively with their illness. Chaplains maintain confidentiality, are held accountable to a certifying chaplaincy organisation as well as the employing institution, and offer compassionate care and concern to all who are in need, regardless of a person's beliefs, religion, or cultural values. For many people, spirituality includes religious practice, but for others applying a contemporary understanding of spirituality may include nature, art, music, family or community. Their spiritual beliefs may allow for an appreciation of the beauty of nature and the world around them, which draws them inward to their deepest core where they discover the resources they need to cope with their illness. Furthermore, chaplains provide one of the greatest gifts one person can give another who is experiencing a severe crisis in their life, and that is a listening presence.

According to chaplaincy staff at Lancaster General Health in Lancaster, Pennsylvania: "Everyone's life is a unique and precious story." Having a calm, compassionate and attentive listening presence to hear a person's story is crucial when one is hospitalised with a serious illness. The experience of sharing one's story and having it truly heard helps to relieve stress and tension, with the possibility of bringing about renewed hope and healing. As the designated chaplain assigned to the palliative care interdisciplinary team, I often describe the chaplain's role as the member of the healthcare team who pulls up a chair at the bedside to listen to a patient's story, providing ethical discernment, requested prayers and/or rituals without an agenda, and usually without time constraints.

Chaplaincy care at NYU Winthrop Hospital

Addressing a need or desire for spiritual support is a part of routine care in the ICUs at NYU Winthrop Hospital, a 591-bed university-affiliated medical centre and New York State-designated Regional Trauma Centre. There are five ICUs: Medical (20 beds), Surgical (23 beds), Neuroscience (14 beds), Paediatric (8 beds) and Neonatal (27 beds). One chaplain is assigned to cover an adult ICU unit and is required to round on that unit daily. The Paediatric and Neonatal units are covered by the chaplain managing the daily code pager, who works closely with the social workers assigned to those units. Contact information for the chaplains assigned to the ICUs is posted on the unit's white board for easy access during daytime hours. After hours, referrals are made for the on-call chaplain through the hospital operator. At the end of each day, the ICU

chaplains provide updates to the on-call chaplain for continuity of care and coverage during the night. Over a six-month period, there were 207 referrals for chaplaincy care in the ICUs (from nurses, patients, family members, other members of the healthcare team, including palliative care). These numbers reflect the commitment, connections and rapport the staff had already established with the chaplains, and the ongoing connections made between the chaplains, patients, and families.

Supporting patients and their families

In addition to making referrals to a patient's spiritual leader, rounding with the ICU healthcare team, and providing a mediating presence for patients—is paramount. As spiritual and religious concerns and perspectives are often tied to how patients experience illness and their end-of-life decision-making, chaplains support patients (and their families) to clearly articulate what they want—or don't want—to members of the healthcare team. Conflict and tension generally arise when the diagnosis, prognosis, and goals of care are not explained in terms that patients can understand. In addition, patients report they are not given time to process the information they have received from members of the healthcare team. The chaplain is often used as a sounding board for staff who may be guided by time constraints, healthcare and government regulations related to the provision of quality care for their patients. As patients struggle to make meaning and purpose of their illness, and attempt to make informed decisions, chaplains can greatly enhance the communication process between patients and staff.

Chaplaincy support offered to families allows the healthcare team to focus on providing treatment and care for the patient without unnecessary and sometimes harmful obstruction from family members. Sensitivity and advocacy on behalf of families is a must. Many patients admitted to the ICU are unconscious, unresponsive, and some will die. The family is often terrified and uncertain about the future of their family without their loved one, who now is unable to communicate, and uncertain of their own future without their loved one. Concerns about financial wellness [and the growing medical costs of ICU care], regrets and confessions are known topics that family members bring to the chaplain. The role of the chaplain becomes one of facilitating a growing list of concerns: mounting tensions among family members, supporting and encouraging end-of-life care decision-making, collaborating with members of the medical team in family meetings and consults, advocating parking passes for extended visitations, or with the dietary department to bring an extra food tray for a long-time spouse who will not leave the bedside of her intubated patient-spouse because she/he, "does not know how else to be, except be by his/her side." The chaplain is also expected to be a "traffic controller" when there are limitations to patient visitations. The communication between the chaplain and members of the healthcare team is invaluable.

Supporting staff

Just as the ICU healthcare team provides patients and family members with education and strategies for improving health and wellbeing on discharge, the chaplain is often requested to help facilitate patient compliance. When a relationship of integrity and trust has been established between the chaplain and patient, outreach to the patient's faith community/spiritual leader with the patient's permission can result in a successful compliance strategy and a lower rate of readmission. Moreover, multidisciplinary teamwork extends to documentation of the chaplain's visit in the patient's medical chart. The chaplain's documentation allows multidisciplinary review of the spiritual assessment, goals of care and changes in the patient's psychosocial-spiritual outlook. Chaplains facilitate an understanding of the role of spiritual, religious and cultural beliefs, values, norms and practices in patient care while at the bedside on the unit. The chaplaincy department can develop and design ICU-specific in-service, didactics and grand rounds as multidisciplinary education opportunities.

The chaplain as a resource of support for staff who need to express existential questions about human suffering, or a safe space to articulate their own vulnerabilities and human frailties after a challenging trauma, or series of traumas on the unit, is in great demand. There are growing data and studies (e.g. "What do I do?" (2017) that suggest the chaplain's time is spent almost equally providing emotional and spiritual support to patients and families, as with members of the healthcare team, especially nursing staff. It is important for members of the healthcare team to care for themselves in order to better care for their patients. In hospitals around the country, administrators are becoming advocates of stress-reduction interventions which help staff regain equilibrium and balance after particularly overwhelmingly traumatic experiences during their patient care.

At Boston Medical Center, for example, staff members gather for a weekly hour of renewal, facilitated by the chaplain, with soft music, light refreshments and massage equipment stations. "We've found that this time helps increase employee morale," notes Chaplain Jennie Gould, PhD. At NYU Winthrop Hospital, staff members on the Oncology unit requested monthly spiritual support at their weekly huddles. Staff chaplains Jackie Lynch, Carol Schneider and Jayan Daniel lead a group activity called, "What's popping?" using popcorn as an edible prop to invite staff to share "what's going on" in their lives. Helping staff to debrief, pause, and take time-outs for just a few minutes of the day, after a "bad", not necessarily, a "sad" incident may lessen an inclination toward burnout, increase the capacity for better self-care, and in the long run improve work productivity."

Chaplains are essential members of the multidisciplinary teams working in the ICU. Their education, training, certification, and skills contribute to the goal of providing whole-person care to seriously ill patients and their families. In addition, they bring much-needed and appreciated expertise to support the various team members who work in constantly stress-filled situations. ■

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Developing new approaches to patient safety

International Society for Rapid Response Systems joins with the Patient Safety Congress in 2018

The International Society for Rapid Response Systems joins with the Patient Safety Congress in July 2018 to develop new approaches to managing patients at risk of deterioration. Identification and treatment of deteriorating hospital patients is a major safety issue and cannot be managed in isolation. This event will bring the issues of the at-risk and deteriorating patient and patient safety closer together.

John Welch
Consultant Nurse
Critical Care & Critical Care Outreach
University College London Hospitals NHS Foundation Trust
London, UK

john.welch@nhs.net

Francesca Rubulotta*
Honorary Clinical Lecturer and Consultant in Anaesthesia and Intensive Care Medicine
Imperial College London, UK

ICU Management & Practice Editorial Board Member

francesca.rubulotta@nhs.net

@frubulotta

The Rapid Response System

The Rapid Response System (RRS) is a primarily clinician-led approach to patient safety across the hospital. It is based on achieving reliable, early identification of at-risk and deteriorating patients and timely delivery of appropriate treatments, with continuous evaluation of processes and outcomes to enable improvement. The impetus for creation of RRSs came from the observation that patients admitted to the ICU from general wards within the hospital suffer far higher mortality than patients admitted from the emergency department or the operating theatre (Goldhill and Sumner 1998). It then became apparent that failures to recognise or act on deterioration are common and a significant contributor to adverse outcomes (McQuillan et al. 1998; Donaldson et al. 2014): among patients triggering a rapid response review in hospitals around the world, 1 in 4 require ICU admission and 1 in 10 die within 24 hours (Bannard-Smith et al. 2016). It has also been found that up to a third of calls for a rapid response actually involve patients at the end of life, so the responding team must be able to provide both aggressive treatments and initiation of end-of-life care (Jones et al. 2013).

New technologies and the EU Nightingale Horizon 2020 project

Early identification of deterioration has been aided by deployment of early warning systems using combinations of vital signs to track patients' acuity of illness and trigger escalation at designated levels of physiological abnormality; for example, the NHS National Early Warning Score, which is formally endorsed as the means to identify acutely ill patients in all hospitals in England (Royal College of Physicians 2017). New technology allows for more sophisticated approaches, and the European Union's Horizon 2020 research and innovation programme is currently sponsoring five major hospitals across the continent to stimulate development of the 'ultimate patient monitoring system'. This Nightingale H2020 project recently had over sixty companies submit tenders to build such systems, with nine consortia selected to go forward to the next phase. These are a mix of multinational companies and small/medium-sized enterprises aiming to use 'real-time' analyses of wireless monitoring of vital signs combined with patient self-reports, laboratory data, demographic details and other information from the electronic health record (see **nightingale-h2020.eu**). The initial focus is on high-risk patients including emergency admissions, major surgical cases and ICU follow-ups; but the ambition is to be able to monitor a whole range of hospital patients and selected patients at home in due course.

> "the RRS can play a leading part in developing a safety-focused culture and patient-safety systems across hospitals"

RRS outcomes

Systematic reviews of RRS effectiveness most consistently find a reduction in cardiac arrests and often a mortality reduction too (Jones et al. 2016). Suboptimal management of patients at risk of deterioration has led to the development of national guidelines and tools for tracking and responding to these situations (Royal College of Physicians 2017; Subbe et al. 2017), but ultimately the clinical skills, decision-making and team-working of healthcare practitioners determine optimal care. It has been demonstrated that the RRS can play a leading part in developing a safety-focused culture and patient-safety systems across hospitals, although it takes time for systems to mature, for barriers to be overcome, and for escalation of at-risk patients and learning from adverse events to become routine practice. An interrupted time series study of nearly 10 million patients in 232 hospitals described a progressive reduction in failures to rescue deteriorating patients, cardiac arrests and mortality from early on, and then also improved outcomes for low mortality diagnostic-related patients in the latter years (Chen et al. 2016; Pain et al. 2017). However, the response cannot occur in isolation and the system cannot survive without integration in an overall patient safety framework.

International Society for Rapid Response Systems

The International Society for Rapid Response Systems (iSRRS) is a global membership organisation committed to being the ultimate knowledge source for those involved in the identification and treatment of deteriorating patients and improvement of patient safety. The society is relatively new, but its founders have a body of work behind them including thirteen international conferences, two textbooks, two consensus conferences and a series of internationally conducted courses on how to establish a RRS. The first consensus conference described

Christian P. Subbe
Consultant Physician
Acute, Respiratory
and Intensive Care Medicine
Ysbyty Gwynedd
Bangor, Wales

Senior Clinical Lecturer in Acute
and Critical Care Medicine
School of Medical Sciences
Bangor University
Bangor, Wales

csubbe@hotmail.com

@csubbe

*corresponding author

Figure 1. Chain of Safety

Source: Subbe CP, Welch JR (2013) Clin Risk, 19(1):6-11.

the essential components of the RRS including data collection and administrative arms to oversee all RRS activities and integrate these into the complex whole hospital environment (DeVita et al. 2006). The core components are methods to reliably *record* key patient data (vital signs, but also laboratory data and demographic information), having clear indicators enabling staff to *recognise* at-risk and deteriorating patients, ensuring timely *report* – or escalation – of deterioration; and a timely, effective *response* (Subbe and Welch 2013): see **Figure 1**.

International Conference on Rapid Response Systems & Medical Emergency Teams

In 2018 the iSRRS is working together with the Health Service Journal and Patient Safety Congress to bring the issues of the at-risk and deteriorating patient and patient safety more generally closer together. The Patient Safety Congress is now in its 11th year and last year brought together over 1000 attendees. It has built a reputation as the UK's best-regarded safety and quality improvement event by developing a high-quality programme in partnership with national and international experts, patients and frontline practitioners. The iSRRS and UK National Outreach Forum's 14th International Conference on Rapid Response Systems & Medical Emergency Teams will be co-located with the Patient Safety Congress and Patient Safety Awards on 9th and 10th July at Manchester Central to deliver a two-day landmark event to help dramatically improve patient outcomes and safety in healthcare.

The 2018 International Conference is the key opportunity for all clinical and managerial staff interested in at-risk and deteriorating patients—together with policy-makers—to discuss international best practice in the field. There will be integrated multidisciplinary expert panels, insights into optimal clinical care of challenging patients, sharing of innovation and improvements from different settings, and a new consensus conference on the metrics needed to evaluate the whole RRS. A shared stream of content and a single expanded exhibition area open to delegates from both events will promote the sharing of ideas between clinicians, patient safety and quality improvement experts from around the world. ■

Note: for International Conference on RRS & Medical Emergency Teams delegate information contact Syed.Ali@wilmingtonhealthcare.com / +44 (0)20 7608 9072.

Websites for more information:

- **rapidresponsesystems.org**
- **rapidresponse2018.com**
- **patientsafetycongress.co.uk**
- **nightingale-h2020.eu**

International Conference on RRS & Medical Emergency Teams: key themes

- World-leading clinicians and researchers discussing best practice and innovation in deterioration and rapid response from Britain, Europe, America, Asia and Australia
- Why hospitals aren't safer: what they must do to be better (clinician-led change, the patient role)
- Managing deterioration from care home to intensive care
- How to make it easy to do the right thing
- Measuring and improving rapid response processes and outcomes
- First reports of new rapid response multicentre studies
- State of the art in critical cases: sepsis, AKI, and other clinical challenges
- Engaging the board and policymakers
- Technology for high-risk patients and Rapid Response Systems: what's new, what's next
- The acute care–end-of-life care interface
- Multiprofessional working
- Optimising education, training and clinical competence
- Specialist care in maternity, paediatrics, cancer and the frail elderly

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How to provide better intensive care?

Systems approach and individualised care

Professor Jukka Takala, MD, PhD, is professor of Intensive Care Medicine in the University of Bern, Switzerland, Director and Chief Physician of the Department of Intensive Care Medicine, and Chair of the business unit of Intensive Care Medicine, Emergency Medicine and Anaesthesiology and Pain Medicine at Inselspital, the Bern University Hospital. His research focuses on the pathophysiology of multi-organ failure, splanchnic tissue perfusion, costs and quality of intensive care, resource use and intensive care organisation. He served as President of the European Society of Intensive Care Medicine from 2000 to 2002 and was awarded the Society Medal in 2014. He has been a member of the Editorial Board of ICU Management & Practice from its first issue in 2000.

There is a school of thought that in intensive care medicine practice should change only with randomised controlled trials. What is your viewpoint on this?

Trials do provide advice for practice change, but if you look at the fine detail our practice has changed a lot without the support of randomised controlled trials (RCTs). Intensive care medicine practice is a learning process. In that sense it's more like craftsmanship where you learn as you go along. Looking at the overall improvement of outcomes in the critically ill patient population over the last 30 years or so there is a major improvement, based on comparing the severity of illness scores developed in the 1980s with the outcome of patients now. In most parts of the industrialised world, the actual mortalities are somewhere between 60-70% of those predicted, i.e. the severity-adjusted outcomes are substantially better than they were 30 years ago. Clearly this is a sign that our practice has improved, and only very little of that improvement is based on RCTs.

Why has it improved?

Firstly we have learned what hurts people, and secondly we have learned, as every craftsman learns through doing his practice, how to get better results. It's the complexity of our patient populations that makes RCTs on single interventions not very useful; they are at their best when they show what does harm.

Is enough attention given to control groups in RCTs?

For RCTs on any disease it is extremely important to evaluate whether the control group in the trial represents your usual practice. I think there has been much too little emphasis focused on the characteristics of the control group, because if your control group receives care, which is not at all consistent with usual care, you cannot draw any conclusions. For example, in our systematic review on septic shock trials from 2006-2016 we found 24 RCTs, which had at least 50 patients in the control group, and we found that only 2 of these trials provided enough data to confirm that the control group treatment represented usual care (Pettilä et al. 2016).

How has having a medical emergency team (MET) benefited your hospital, Inselspital? What challenges did you face when you introduced it?

We had the usual challenges of any MET system, which is to obtain access to patients not directly under the team's treatment. There are often obstacles from the primary specialities who take care of patients to allow access from a different team. However, we first assessed the size of the problem in our own hospital. Once we had those numbers it was fairly easy to convince the other departments that there are problems which can be met by the MET team. The MET team was introduced first as a project, was formally evaluated afterwards, and when we presented the results, there was overwhelming support from all departments to continue to establish it as a productive system (Etter et al. 2014). We have now had it almost 10 years and the number of emergency admissions from the wards has been reduced substantially. In-hospital cardiac arrests decreased and the outcomes for patients who are admitted from the normal wards to the ICU are no different from those patients who come as emergencies directly to the ICU. This was not previously the case. It shows that the earlier recognition of problems in these patients brings them faster to the ICU. What is also important is that only half of the patients with a MET call need to come to the ICU. With the other patients problems can be resolved at the bedside.

The clinical prediction model for identifying patients at high risk of death in the emergency department that was developed at your hospital performed better than non-systematic triaging. Has the model been externally validated or implemented at your hospital?

We created a prediction model for ED patients (Coslovsky et al. 2015), which has not been externally validated, but we

have taken it to use in a slightly modified form in the usual triage practice in the ED and it has been very welcome. The simple signs that tell you that an intervention by a doctor is urgently needed have really helped the practice.

Your research has found that despite considerable variability in outcome and resource use only few factors of ICU structure and process are associated with efficient use of ICU and that this suggests that other confounding factors play an important role (Rothen et al. 2007). Please comment.

This evaluation is based on the variable that we created, the standardised resource use (SRU). This means that we can estimate the resources used to produce a surviving patient and by adjusting this for the severity of the patient, we can calculate the SRU, which is the economic equivalent to the standardised mortality rate (SMR). It shows how many resources are needed for a severity-adjusted survivor. If we look at studies using the SMR which look at the factors predicting the differences, they can perhaps find variables explaining up to 40% of the variability in the SMRs. What is even more intriguing is that if you look at the resources, the differences there are much higher. The SMR may be 2-3 times different between units in a similar healthcare system, but even in a very homogeneous healthcare system you can see up to a 6-times difference in SRU. The way we manage these patients and the resources we need to provide survivors from patients of similar severity is extremely variable, and it makes the cost of ICU care highly variable.

How do you go about investigating it?

It is difficult. We are currently doing a study, which includes about 35 ICUs in three countries. We will look at the structures in detail, how the units operate and the staffing—how it's allocated, the on-call, night-time and late day duty systems, and the availability of specialists. We will then investigate the individual components of cost in great detail. We have access to drug and materials use, personnel costs and so on. We want to find out variables which could be associated with better performance, both economically and in terms of survival.

"only half of the patients with a met call need to come to the icu"

How can technology help improve ICU quality in real time?

One of the key issues is that we can detect evolving disorders and complications in organ functions earlier than we do today. There are different ways to approach it. One is to make the evolution of patients over time better visible. That can be used with fairly simple technology providing the display of data we have in a context-sensitive format. Of course it uses information technology, but it's really rudimentary because we are taking the data that is already available, just displaying it better and combining it for better interpretation. In the future we will have artificial intelligence that will help to detect changes earlier and bring the doctors to patients earlier than they would do when they just notice a disorder that has already manifested itself. That's where there is great potential, and I am sure that we will see more and more intelligence implemented in these patient data management systems in the near future.

What is the ideal practice for sedation in the ICU?

The ideal is to sedate as little as possible and keep the patient awake when it's possible for the comfort of the patient. Of course we need to be selective and individualise sedation so that patients who are so unstable that their being awake may further compromise their vital functions do receive sedation. The best approach is to provide comfort. The eCASH position paper summarises the main principles: compassionate care with focus on patient comfort, analgesia, minimal sedation, good communication between the patient and care team and family (Vincent et al. 2016). There is nothing that could be perceived as a magic solution for sedation problems, but we have come to understand much better that being deeply sedated is not the comfort that we should be providing for patients, but being awake and without pain is mostly the best status for the patient. If they need some support, for example for normalising sleep, we can of course provide that, but many patients prefer to be awake, without pain.

There is more emphasis now on tracking long-term outcomes of ICU survivors—moving beyond 28-day mortality. You've noted that such outcome data is not readily available in Switzerland for data protection reasons. How might that hold back research?

I am pleased to say that this has just changed, and we have access to non-survival data. Deaths can be accessed and recorded. We are just implementing that into our clinical data warehouse in the hospital so we can follow up long-term outcomes of patients. It is extremely important. We know from previous trials in general populations that if ex-patients are alive one year after discharge from hospital then mortalities have traditionally approached those of the age and sex-matched general population. Nowadays when more and more sick patients survive, this may be very different, and therefore the assessment of excess mortality post-ICU stay is a very important component to evaluate whether we are doing the right thing or not.

The ability to promote adaptive learning is the challenge for leadership: how to guide team members through problem solving with motivation and confidence, rather than autocratically dictating a solution (Zante et al. 2016). As an ICU director, how do you achieve this in your own department?

I think you could have different answers from my staff and myself! The main issue is to make sure to understand the difference between discussions on the patient data, the patient's clinical course and what we have done versus what is being perceived as personal criticism or evaluation. We are in the business of trying to save lives. We need to be very open and critical about what

we have done and what we plan to do for patients. Since there is seldom only one solution we have to keep our eyes open so we do the best for what is in the interest of the patients. Sometimes it can be a conflict between individuals' preferences and what is good for the patient, or what is good for the department. It's one of the most difficult challenges in the ICU, and I am not at all sure if I have the answer.

You have argued for rethinking resuscitation endpoints and moving to permissive hypotension and a tissue perfusion-based approach (Dünser et al. 2013). Please comment.

The issue is that if we take a fixed target value of any physiologic variable, e.g. blood pressures, for all patients, we end up with over-treating some patients and under-treating others. We have pretty much overlooked the potential of our cardiovascular support to cause harm to our patients. What we have observed in our clinical practice is that patients are reaching what I would say are clinical endpoints of being stable with values for different variables that are often much lower than what are recommended in guidelines. We have taken the approach that we are trying to assess how the resuscitation or haemodynamic support based on simple clinical variables can perhaps end in better outcomes than just resuscitating patients with fixed numbers. It's amazing that if you look at most clinical trials on septic shock, for example, everybody does something else than what is predicted by the protocols. So for example blood pressure targets have never been investigated properly—it makes much more sense to tailor treatment per patient rather than for a fixed number.

In relation to the clinical significance of monitoring perfusion in non-vital organs you've suggested that reliance on simple methods, such as capillary refill time, skin temperature and mottling score, must be emphasised and exploited (Lima and Takala 2014).

First of all I want to bring the doctor to the patient to make a clinical assessment. Secondly, what we have learned is that as far as the patient's peripheral perfusion is good, overall tissue perfusion is unlikely to be a problem. Those are easily available clinical tools that we can bring everywhere as quickly as possible, and the nursing staff can use these to monitor patients.

Giving volume to fluid responders as long as they respond should not become the iatrogenic syndrome of the decade; the same is true for failure to give volume to fluid non-responders, who need fluids to maintain their stressed volume while restoring perfusion of vasoconstricted vascular beds (Takala 2016). Please comment.

The use of what we call dynamic haemodynamic variables has resulted once again in a simplistic approach. If you see variation in blood pressure people tend to believe that these patients are a) volume responders and b) they need volume. Both of them are not true, because basically the physiology is more complex. You can have the same variables reflecting completely different phenomena such as fluid responsiveness in patients with hypovolaemia versus right ventricular dysfunction in patients with for example sepsis or septic shock. If we uncritically just give fluids to all these patients we will do something which is harmful, especially because being fluid responsive is a normal status. Giving fluids to all "fluid responsive" patients until they become fluid unresponsive creates a new pathology—many of these patients do not need additional fluids. ■

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Caring for critically ill immunocompromised patients

We can do better!

Élie Azoulay, MD, PhD, is Professor of Medicine in Specialty Pulmonary Medicine and Critical Care at Saint Louis Teaching Hospital and Université Paris Diderot in France. He is the Director of the medical intensive care unit (ICU). He leads the French programme for the care of critically ill immunocompromised patients, and is part of the national reference centre for thrombotic microangiopathies. In 2005 he established a research network, the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH), to improve practices in critically ill patients with malignancies. GRR-OH includes more than 30 ICUs in France recruiting a high volume of immunocompromised patients. In 2014 GRRR-OH experts joined multinational experts to create the Nine-i (Caring for Critically Ill Immunocompromised Patients, Multinational Network), whose aim is to improve the care of critically ill immunocompromised patients. Professor Azoulay is also Director of the French FAMIREA study group aimed at improving effectiveness of communication with family members of ICU patients. He serves as Editor-in-Chief of Intensive Care Medicine.

What are the major challenges in treating critically ill immunocompromised patients?

Thank you for starting with the most important question. It is now demonstrated that critically ill immunocompromised patients are sicker and exhibit higher mortality rates compared to general intensive care unit (ICU) patients. However, managing these patients requires some knowledge related to the underlying disease (this group is highly heterogeneous), related treatments (time before effectiveness, patterns of toxicity, alternative regimen), specific emergencies (i.e. tumour lysis syndrome, cytokine releasing syndrome or acute humoral rejection), or specific clinical vignettes (febrile neutropenia).

There are two other challenges in treating immunocompromised (IC) patients: the first is to know how to work closely with referring clinicians (haematologists, oncologists, transplant specialists), and the second is to apply to IC patients all recent diagnostic and therapeutic advances validated in non-IC patients (in studies where IC patients were mostly excluded).

Is it clear which immunocompromised patients will benefit from intensive care?

Let me answer the other way. It is clear that some patients cannot benefit from intensive care. These are patients who have a very poor performance status (bedridden or dependent) and those in whom no lifespan expanding therapy is available. Here, patients have to be managed together with the palliative care team, and ICU admission is non-beneficial. In all other situations, ICU management can benefit immunocompromised patients, but the goals of care are of course different from one situation to another.

When you look at 100 patients, who are admitted to our ICUs, 80 have a full code status, 15 are undergoing a time-limited trial, and 5 may have other goals such as palliative ICU admission (noninvasive ventilation or high flow oxygen in patients who are 'Do Not Intubate') or exceptional ICU admission (patients with advanced disease receiving newly released biotherapy, immunotherapy or any targeted therapy).

When should immunocompromised patients be admitted to ICU?

Patients should be admitted early enough to be able to undergo a noninvasive diagnostic or therapeutic strategy. Several studies have shown that delayed ICU admission was associated with higher mortality. For example, in a study from our group, mortality doubled from 20 to 40% in patients who were admitted after day 3 of the onset of the acute respiratory failure (Mokart et al. 20013).

Are there adequate triage criteria?

Triage criteria are not reliable and clinicians need to be aware that patients with limited goals of care can benefit from ICU admission, even when it comes to outcomes such as mortality or quality of life. At the same time, studies have shown that when death occurs in the ICU, both patient and family burden are among the highest possible. Thus we do not encourage ICU admission for patients with irreversible conditions or when death is the only expected outcome.

Should there be guidelines?

It is certainly time to release international guidelines for the standard of care to manage critically ill immunocompromised patients; nothing is available to date.

What has led to improved care of immunocompromised patients?

I would classify these into three different domains:

Advances in the care of IC patients overall

We know that the number of averted deaths from cancer is huge and increasing: today 5% of the population is a cancer survivor. The number of new steroid-sparing agents in transplantation, chronic inflammatory or autoimmune diseases is growing, so that these diseases are much better controlled.

Advances in the management of general ICU patients

We are all enthusiastic for positive trials and are upset when physiology or observation-driven interventions fail to improve outcomes. Nevertheless, over the last two decades, adjusted mortality has decreased in patients with acute respiratory distress syndrome (ARDS), sepsis or acute kidney injury (AKI). However, with changing definitions of ICU syndromes and varying case mix, this remains controversial.

"patients should be admitted early enough to be able to undergo a noninvasive diagnostic or therapeutic strategy"

Several advances in the ICU management of IC patients have translated into improved survival.

Namely, noninvasive diagnostic and therapeutic strategies have allowed faster and safer management of patients with acute respiratory failure, typhlitis or other sources of sepsis. Also, a better understanding of organ dysfunction at the earliest phase of haematological malignancies has helped manage the patients with a more targeted way. Other advances include early admission to the ICU, antibiotic stewardship, antifungal prophylaxis, management of drug-related toxicity etc.

What can further improve outcomes for and survival of immunocompromised patients? What should the research priorities be?

There is a large margin for improvement. For instance, we can expect a lot from diagnostic strategy in acute respiratory failure, from fluid management, antibiotic de-escalation and combination, transfusion policies, as well as for specific management of patients with neutropaenia and sepsis from undetermined source. We should move away from ideas that oxygenation and ventilation management are going to save lives, that intubation is always mortal, or that the ICU is a bad place to start chemotherapy. In the September issue of *Intensive Care Medicine* we published a research agenda in oncology and haematology patients (Azoulay et al. 2017). Worldwide experts have shared their opinions about research priorities in this area of critical care, and this review article summarises these issues very well.

Should immunocompromised patients be treated only at high-volume centres?

The answer has to be no. For several reasons. First, with the growing number of cancer survivors and the numerous toxic events with immunotherapy, it is likely that the number of cancer patients admitted to the ICU will grow significantly. Also, in patients with transplants or chronic inflammatory diseases, age increases steadily over time. Overall, every ICU clinician should acquire skills to manage IC patients. We are now developing a telemedicine programme where experts guide management of patients remaining in low-volume centres. In the close future, alternatives to patients' referral to high-volume centres will develop. Everything should be done to maintain patients where they are, unless of course they need to receive urgent chemotherapy and the centre cannot do it, or if it's a complication related to the transplant, in which case the patient needs to be transferred to the referring centre.

How can oncologists, haematologists, infectious disease specialists and intensivists best work together for better outcomes for immunocompromised patients?

They are committed to do so. They have the same goals: improving the care of IC patients, and not only when they become critically ill. They have to learn from each other and develop collaboration in both clinical and translational research. A paper from Brazil that was published last year reported that when haematologists, oncologists, clinical pharmacists and intensivists were working closely together and discussing the patient's management on a daily basis, this was associated with reduced mortality (Soares et al. 2016). Over the last few years, critical care management of IC patients at high risk of being critically ill has become the rule. This is true at the earliest phase of sepsis and of respiratory events; it is also true in patients with high tumour burden such as hyperleukocytic leukaemia or bulky lymphoma and with the fantastic expansion of targeted therapies.

Are intensivists well-prepared for this increasing group of patients—is current training and education sufficient?

There is an increasing awareness that among patients admitted to the ICU, the first comorbidity will be cancer and other sources of immunosuppression. Critical care curricula are increasingly including specific training. Also ICU specialists are seeking to improve their skills managing these patients. Last, it is very likely that in the hospital of tomorrow, hospital wards and specialists will not be able to manage high-risk patients. ICU specialists will have to learn and to be prepared.

The Efraim cohort study found an association between failure to identify acute respiratory failure (ARF) aetiology and higher rates of intubation and mortality. Please comment.

The Efraim study was a fantastic collaborative work from the Nine-I (Azoulay et al. 2017b). 1611 acute respiratory failure (ARF) patients from 16 countries (68 ICUs) were enrolled and followed until day 28. This study is unique for several reasons: it is the only multinational study on ARF in immunocompromised patients and is the largest study to date. It is a high-quality study with few missing variables and the analysis allowed identification of both risk factors for intubation and mortality. The finding that oxygenation/ventilation strategies have no impact on mortality, but that ARF from undetermined aetiology is associated with both intubation and mortality, allows appraisal of the literature and putting the patient at the right place. It opens avenues for further research. In addition to this published paper, several substudies are about to be submitted.

The Early non-invasive ventilation for acute respiratory failure in immunocompromised patients (IVNIctus) randomised controlled trial appeared to rule out noninvasive ventilation as a therapy for immunocompromised patients with acute respiratory failure (ARF), although the study was underpowered. Please comment.

This multicentre randomised controlled trial (RCT) published in 2015 showed no benefit (and no harm) from noninvasive ventilation (NIV) in IC patients with ARF (Lemiale et al. 2015). It helps to reserve NIV to hypercapnic ARF and pulmonary oedema. We are not using NIV anymore in hypoxaemic ARF, more especially now that in more hypoxaemic patients the Frat trial (Frat et al. 2015) and the Lungsafe study (Bellani et al. 2016) both reported that in the most severely hypoxaemic patients NIV was associated with mortality. We then do not recommend the use of NIV in immunocompromised patients with hypoxaemic ARF. We also do not consider that NIV is a safe comparator in trials. We state so, being aware that perhaps the use of continuous NIV, or continuous positive airway pressure (CPAP) using the helmet, may be beneficial for some patients. Until large studies have demonstrated benefits from these techniques, we recommend not delaying intubation in patients failing standard or high flow oxygen.

What is the HIGH trial A Randomised Controlled Trial of High-Flow Nasal Oxygen Versus Standard Oxygen Therapy in Critically Ill Immunocompromised Patients (HIGH) designed to investigate?

We have just ended recruitment in the HIGH trial (NCT0273945 - clinicaltrials.gov/ct2/show/record/NCT02739451. In this trial that recruited 778 patients from 31 ICUs in France standard oxygen was compared to high flow oxygen. The primary endpoint is day 28 mortality. ■

Abbreviations

ARF acute respiratory failure

IC immunocompromised

ICU intensive care unit

Nine-i Caring for Critically Ill Immunocompromised Patients

Multinational Network

NIV noninvasive ventilation

RCT randomised controlled trial

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AGENDA

For a full listing of events visit https://iii.hm/aly

APRIL

5-7	14th Emirates Critical Care Conference Dubai, UAE **https://iii.hm/hud**
12-14	ESICM EuroAsia 2018 Hong Kong, **https://iii.hm/hue**
12-15	14th WINFOCUS World Congress on Ultrasound in Emergency & Critical Care Madrid, Spain **https://iii.hm/huf**
26-27	15th Annual Critical Care Symposium Manchester, UK **https://iii.hm/hug**

MAY

3-5	ESICM LIVES Forum - Monitoring in ARF Madrid, Spain **https://iii.hm/huh**
9-11	29∞ Smart Meeting Anesthesia Resuscitation Intensive Care Milan, Italy **https://iii.hm/hui**
10-12	3rd Dubai International Conference on Infectious Diseases and Vaccination (DICID) 2018 Dubai, UAE **https://iii.hm/huj**
17-21	5th SG-ANZICS Asia Pacific Intensive Care Forum Singapore **https://iii.hm/huk**
18-23	American Thoracic Society 2018 San Diego, USA **https://iii.hm/hua**
23-25	6th ERAS World Congress Stockholm, Sweden **https://iii.hm/hul**
23-26	7th EuroELSO Congress on ECMO-ECLS Prague, Czech Republic **https://iii.hm/hum**
29-30	Metabolic and Nutritional Issues in the ICU - 2018 Brussels, Belgium **https://iii.hm/hun**

JUNE

2-4	Euroanaesthesia Copenhagen, Denmark **https://iii.hm/huo**
4-8	NeuroIntensive Care: Update 2018 Como, Italy **https://iii.hm/hup**
9-12	41st Annual Conference on Shock Scottsdale, AZ, USA **https://iii.hm/huq**
9-13	9th World Congress of the World Federation of Pediatric Intensive and Critical Care Societies Singapore **https://iii.hm/hur**
10-12	The Future of Critical Care - Brainstorming Meeting Edinburgh, UK **https://iii.hm/hus**
12-15	36th Vicenza Course on AKI & CRRT Vicenza, Italy **https://iii.hm/hut**
14-15	4th World Congress and Exhibition on Antibiotics and Antibiotic Resistance Barcelona, Spain **https://iii.hm/huu**
28-29	Neurosciences in Intensive Care International Symposium 2018 (NICIS) Paris, France **https://iii.hm/huv**

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