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INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY
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Shock

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Clinical challenge in the ICU – identification and monitoring

Bernd Saugel (Hamburg, Germany)
When do we need hemodynamic monitoring?

Frédéric Michard (Lausanne, Switzerland)
Fluid responsiveness – measurement technology in ED, OR and ICU

Marit Habicher (Giessen, Germany)
Successful implementation of optimized fluid management

Tuesday 23rd of October

Future practice in hemodynamic monitoring

12:30 – 14:00 / Room Geneva

Chairmen
Maurizio Cecconi (London, UK) and
Ignacio Monge Garcia (Jerez, Spain)

Bernd Saugel (Hamburg, Germany)
Clinical impact of hypotension

Bart Geerts (Amsterdam, The Netherlands)
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SHOCK

Shock is an emergency, and if it is not treated, it will mostly be fatal. Early intervention and admission to the ICU is essential. Our cover story considers several aspects of shock, including pathophysiology and multi-organ dysfunction syndrome, as well as source control, fluids, differentiation using point-of-care ultrasound and vasoactive medication.

Francesco Forfori, Greta Giuliano and Gabriella Licitra elucidate the pathophysiology of endotoxic shock and the role of endotoxaemia. They suggest that although there are conflicting results from clinical studies on techniques to remove endotoxin, selected subgroups of patients could potentially benefit from their use.

Fluids are a key treatment for shock. Antonio Messina, Massimiliano Greco and Maurizio Cecconi explain which fluids, when, how much and how often. They emphasise that fluids should be administered after testing preload dependency and with continuous evaluation of preload dependency/CO response, together with timely monitoring of clinical and metabolic signs of shock. Fluid stewardship is also important, and Manu Malbrain, Todd Rice and Monty Mythen introduce a conceptual framework for institutional programmes and guidelines to enhance fluid stewardship, which includes appropriate selection, dosing, duration, de-escalation, and monitoring of fluid therapy.

Vasoactive medication is a cornerstone in shock treatment. Jon Gutteling and Armand R.J. Girbes outline the physiology and pharmacology of vasoactive drugs and explain how to decide on drug dose, the haemodynamic values to pursue, and how much fluid to infuse, by introducing the concept of "enough" for different cardiovascular parameters.

In the critical first hour of sepsis treatment, source control receives little attention, according to Jan De Waele and Ignacio Martin-Loeches, but should be considered. They outline the challenges, methods and timing. Next, John Prowle expands on the concept of 'organ cross-talk', which is often used to explain multi-organ dysfunction syndrome.

Point-of-care ultrasound is a useful tool to differentiate and manage shock. Adrian Wong and Jonathan Wilkinson provide an overview of how the various POCUS modules could be integrated and utilised in the shocked patient.

Our Series on Gases continues with a review by Mervyn Maze and Timo Laitio of the latest research on xenon, which shows promise in treating acute CNS injury, including after cardiac arrest.

In European ICUs, up to 15% of patients may be aged 80 or over, and this age group is increasing in the general population. Hans Flaatten reviews the outcomes for these patients and outlines geriatric syndromes that intensivists should be aware of as well as specific ICU care. Achieving good sleep in the ICU depends on many factors. Michael Reade and David Liu review how to achieve better sleep, including pharmacological and non-pharmacological treatments. Non-pharmacological methods to improve sleep are almost always preferable first-line alternatives in critically ill patients, they emphasise.

To admit or not to admit cancer patients to the ICU has been a dilemma in the past. As cancer treatments become more effective, thus improving prognosis, it is likely that the number of cancer patients requiring admission to ICU will continue to increase. Isidro Prieto del Portillo, Ignacio Sáez de la Fuente and Pujol Varela apprise us of key elements for successful patient management: new anti-tumour therapies, admission criteria, improved support measures in ICUs and ICU trial stays.

There is a medical aphorism "Don't just stand there, do nothing!" Do we sometimes do too much or continue with interventions that no longer benefit? Fernando Zampieri argues that intensivists should acknowledge that they are prone to several cognitive biases and asks "What should we stop doing in the ICU?"

Next, Elisabeth Esteban, Anna Solé-Ribalta, Iolanda Jordan expound on the diagnosis and treatment of sepsis in children. Rapid response to sepsis is crucial. But does having pre-prepared components, such as a sepsis box, assist? NHS Wales trialled and evaluated this, as described by Chris Hancock and Andrew Hermon.

In the multidisciplinary ICU team, increasingly psychologists are employed to work with patients, families and staff. Anne Rocher describes an initiative to train clinicians to break bad news and communicate with families about limiting therapy and transitioning to comfort care.

ECMO is feasible outside large academic hospitals, writes Klaus Kogelmann. Before setting up this service, centres should consider which patients, which therapy and which adverse events could be handled.

Our Interview features Jannicke Mellin-Olsen, President of the World Federation of Societies of Anaesthesiologists. When 5 out of 7 billion people do not have access to safe, timely affordable anaesthesia and surgery, anaesthetists need to lead and create awareness, advocate, educate and set standards, she says, as well as sharing her thoughts on ketamine, gender equity and airway management. ■

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

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COVER STORY

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COMPLEMENTARY THERAPIES IN ENDOTOXIC SHOCK: THE POLYMYXIN B HEMOPERFUSION

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Polymyxin B Hemoperfusion During Emergency Abdominal Surgery: Rationale and Application
Pugin J. (Geneva, Switzerland)

Targeting a Complementary Therapy for Endotoxic Shock: What we have Learned from Literature and Clinical Experience
Antonelli, M. (Rome, Italy)

High Dose Vasopressor Refractory Shock and Role of Polymyxin B Hemoperfusion Therapy
Monti, G. (Milan, Italy)

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Pathophysiology of endotoxic shock

Mechanisms of endotoxin-induced multi-organ damage

Endotoxin-induced sepsis remains a leading cause of mortality in intensive care units (ICUs) worldwide. Lipopolysaccharide (LPS) identification by the immune system triggers a cascade of signalling pathways, leading to the release of several cytokines and chemokines, which orchestrate the anti-microbial and inflammatory response, though causing multiorgan damage as well. Furthermore, endotoxin is involved in the alterations of the innate and adaptative immune system, which are of utmost important in the development of immune-paralysis in sepsis and may contribute to sepsis late mortality. Even if clinical studies on techniques aiming to remove endotoxin have yielded conflicting results so far, it seems that selected subgroups of patients could benefit from their use.

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Sepsis remains a leading cause of mortality in ICUs worldwide (Vincent et al. 2009) and is considered a global health priority (Reinhart et al. 2017). In 2016, new definitions and criteria of sepsis, underlining the utmost importance of the non-homeostatic host response to infection in the development of this syndrome, were published (Singer et al. 2016).

Sepsis incidence is rising due to several reasons and treatment is becoming increasingly difficult because of the spreading of multidrug-resistant bacteria. The number of Gram-negative infections in ICU is progressively increasing. In 2007, 62% of the positive isolates in ICU patients were Gram-negative organisms (Vincent et al. 2009); moreover the mortality for Gram-negative bacteraemia is higher than that for Gram-positive (Cohen et al. 2004).

Endotoxins as PAMPs

Endotoxin (LPS) is probably the most important trigger of inflammatory response in Gram-negative infection. It is a three domains essential component of the cell wall of Gram-negative bacteria and it has a highly conserved structure (Opal and Gluck 2003). However, it is the 'regulated host response' to LPS, rather than the intrinsic properties of LPS itself, which is responsible for the potentially lethal consequence attributed to this mediator (Monti et al. 2010).

The innate immune response is the first line of defence against infections and is based on recognition of pathogens structures, termed pathogen-associated molecular patterns (PAMPs), which are vital for survival of microorganisms and have consequently remained immutable over millennia. When PAMPs, such as LPS, peptidoglycan and lipoteichoic acid of Gram-positive bacteria, fungal glucan, (Marshfield 2011) bind to the so-called pattern recognition receptors (PRRs), the proinflammatory and antimicrobial response is triggered. It is noteworthy that also host fragments altered by cellular stress are equally recognised by the PRRs as "danger" signals, termed damage-associated molecular patterns (DAMPs) (Mogensen 2009).

Toll-like receptors (TLRs) are the family of PRRs that have been studied more thoroughly. Currently, ten TLRs have been described. TLR-4 interacts with LPS and HSP (Opal 2010; Saha et al. 2010). LPS, through LPS binding protein, binds to the complex CD14/TLR4/MD2, which is expressed on the cell surface on both immune and non-immune cells (Molteni et al 2016). Then, two different pathways of cellular activation can occur through either the MyD88 (myeloid differentiation factor 88), which mediates the early activation of nuclear factor κB (NFκB), leading mainly to the synthesis of pro-inflammatory cytokines (TNF-α, IL1B, IL-6, IL12B), or the TRIF (Toll-like receptor domain adaptor inducing interferon-β), which, on the other hand, is involved in the late phase of transcriptional activation (IL-10) and in the development of endotoxin tolerance (Biswas and Lopez-Collazo 2009) (**Figure 1A**).

Clinical relevance of LPS

The most clear-cut example of the relationship between endotoxaemia and outcome is meningococcal disease (Cohen 2000). Even if this relationship is much more difficult to demonstrate in a heterogeneous ICU popula-

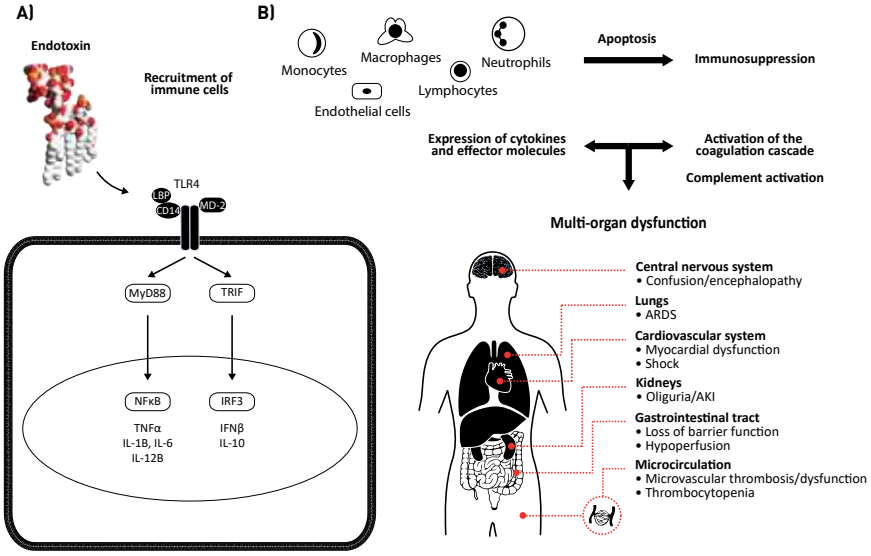

Figure 1. Schematic representation of pathophysiology of endotoxin sepsis A) After the binding of LPS to CD14 and then TLR-4/MD-2, two not mutually exclusive pathways can be activated. B) The activation of the immune system can lead both to multiorgan damage and to immunosuppression (see text)

tion, several studies have highlighted the role of endotoxaemia on progression and outcome of sepsis and septic shock (Danner et al 1991; Opal et al 1999).

In 2004, the MEDIC study, enrolling 857 ICU patients, was the first large observational cohort study to correlate endotoxin level, measured by endotoxin activity assay (EAA), with mortality. Rates of severe sepsis were 4.9%, 9.2%, and 13.2%, and ICU mortality was 10.9%, 13.2%, and 16.8% for patients with low, intermediate, and high EA levels, respectively (Marshall et al. 2004). Similarly, in a prospective study, Monti et al. (2010) showed that 'high EA level septic shock patients' were in need of a significantly higher vasopressors dose than intermediate and low EA groups with increased hospital mortality.

Interestingly, EA is not detectable only in patients with Gram-negative infection. More than 50% of patients admitted in ICU have intermediate or high levels of EA as compared to healthy volunteers; however, only 4% of this population had a documented Gram-negative infection (Monti et al. 2010). It has been hypothesised that the reason behind endotoxin increase in those patients is the gut barrier dysfunction (Esteban et al. 2013) associated with splanchnic hypoperfusion or gut permeability changes (McIntyre et al. 2011; Klein et al. 2007).

Pathophysiology of organ damage in Gram-negative sepsis

Endothelial dysfunction and the consequential barrier disruption leading to increased vascular permeability is critical to the pathogenesis of multi-organ failure in sepsis (Winkler et al. 2017). Specifically, stimulation of endothelial cells with LPS leads to the upregulation of several adhesion molecules (E-selectin, P-selectin, intercellular adhesion molecule-1, etc), cytokine (IFN-α, INF-γ, IL-6) and chemokine (CCL2, CCL3, CCL5). Moreover, endotoxin decreases the expression of thrombomodulin, tissue-type plasminogen activator and heparin, while increasing the expression of tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1), thus shifting the haemostatic balance from an anticoagulant to a procoagulant state. Systemic infusion of low dose LPS in healthy humans results in an enormous rise in TF mRNA levels in mononuclear cells causing thrombin generation and further haemostatic activation (Levi and Sivapalaratnam 2018). Furthermore, LPS-induced apoptosis of endothelial cells, exposing prothrombotic subendothelial proteins to clotting factors, further tilts the balance towards a procoagulant state (Seeley et al. 2012).

After an LPS challenge or sepsis insult, the heart may become dysfunctional, exhibiting a "stunning"-like profile characterised by a diffuse and reversible decrease in ejection fraction with enlargement of ventricular diameter/volumes (Chagnon et al. 2005), associated with altered muscle compliance (Chagnon et al. 2006). Microscopically, reversible and irreversible cytopathologic basic alterations include apoptosis, focal necrosis, congestion, inflammatory infiltrates, and oedema (Chagnon et al. 2006). The impairment of cardiac function during sepsis is due to several mechanisms (Flesch et al. 1999), which have not been exactly clarified yet (Yucel et al. 2017). A controversial hypothesis proposed to explain sepsis-induced cardiac dysfunctions is inadequate coronary blood flow (Chagnon et al. 2006). In fact, some studies in animals have showed that coronary blood flow is reduced by infusion of endotoxin. On the other hand, others reported a marked coronary vasodilation and even higher coronary flow in patients with sepsis (Yucel et al. 2017). Furthermore, numerous chemical mediators such as tumour necrosis factor alpha (TNF-α), MIF, interleukin-1, nitric oxide and reactive oxygen species (ROS) have been widely implicated in the pathogenesis of sepsis-induced cardiomyopathy (Chagnon et al. 2006; Yucel et al. 2017). Apoptosis seems to play an important role as well (Chagnon et al. 2005; Lancel et al. 2005). In detail, not only may endotoxin trigger heart multiple caspase activation and cytochrome c release from the mitochondria causing end-stage apoptosis of myocardial cells, but caspase-3 activation may also directly cause changes in calcium myofilament response, in troponin T cleavage, and in sarcomere disorganisation, without inducing myocardial cell death (Lancel et al. 2005). Also myocardial wall oedema per se can be an underestimated component of this reversible dysfunction altering myocardial compliance and elastance (Chagnon et al. 2006).

The frequent cardiac rhythm alteration in septic patients may be partially explained by the evidence of action potential duration (ADP)-prolongation in human pluripotent stem cell treated with LPS (Yucel et al. 2017).

LPS infusion is often used to recreate ALI (acute lung injury) in different species (Waerhaug et al. 2008). In animal models, after 1 hour from intratracheal instillation or intravenous infusion, considerable tissue injury can be observed, and it is characterised by neutrophil accumulation in the alveolar and interstitial space, alveolar wall thickening, accumulation

of proteinaceous oedema and detritus in the alveolar space (Matute-Bello et al. 2011). These alterations are mostly due to the presence of profound vascular leakage causing not only movement of fluid and macro-molecules into the interstitium and airspace, but also transendothelial diapedesis of leukocytes into lung tissues, further contributing to vascular and alveolar dysfunction (Peng et al. 2004). Another important feature of ALI is the formation of microthrombi (Proudfoot et al. 2011) and alveolar fibrin deposition that, due to the extensive cross-talk between coagulation and inflammation, may further inflame the lungs (Tuinman et al. 2012). Futhermore, Rodriguez-Gonzalez et al. (2015) showed that inflammatory mediators released during LPS-induced lung epithelial cell injury might contribute to the development of septic-associated encephalopathy.

The pathogenesis of LPS-induced acute kidney injury (AKI) in humans is complex and it is not simplistically related to hypoperfusion and ischaemia (Morrell et al. 2014a; Nakano et al. 2015). In the kidney, as well as in the lung and in the heart, TLR-4 is constitutively expressed on tubular epithelial cells (especially within the apical brush border of proximal tubules) (Morrell et al. 2014a). Unfortunately, so far, little is known about the final downstream mechanisms that produce AKI after TLR-4 activation and the start of the intracellular signalling cascades (Morrell et al. 2014a). In a recent review, Morrell et al. (2014b) have suggested that the inflammatory pathway can induce renal tubular transport dysfunction with enhanced NaCl delivery to the macula densa and increased tubule-glomerular feedback, impairing the glomerular filtration rate (GFR). A study on LPS-induced AKI in mice showed LPS selectively accumulated in proximal tubule cells through a TLR-4 dependent mechanism, associated initially with a reduction in tubular flow rate and then with cells swelling and tubular obstruction (Nakano et al. 2015). Additionally, apoptosis has been proposed to play a role in the pathogenesis of septic AKI, probably through the TNFR1 (Tumor Necrosis Factor Receptor 1), as supported by a study where TNFR1−/− mice had less apoptosis in renal cells and fewer neutrophils infiltrating the kidney following LPS administration compared with TNFR1+/+ (Cunningham et al. 2002). Nonetheless, a recent study shows that LPS can also directly cause apoptosis of tubular cells through Fas-mediated and caspase-mediated pathways (Cantaluppi et al. 2008). Moreover, LPS can directly act on kidney-resident cells such as podocytes and tubular epithelium, stimulating the synthesis of inflammatory mediators (Zurovsky et al. 1995) (**Figure 1B**).

Endotoxin and the immune system

Due to improvements in intensive care management, early sepsis mortality has gone down during the last decades. However, late mortality is soaring. The alterations in innate and adaptive immune system induced by sepsis are thought to be of paramount importance in long-term mortality (Delano and Ward 2016).

Experimental models of sepsis have been widely used to study the so-called endotoxin tolerance, that is the desensitisation to endotoxin-induced lethality after a priming (small) dose of endotoxin before an otherwise lethal challenge dose of endotoxin. It probably occurs also in human Gram-negative sepsis (Opal 2007). The concept of 'endotoxin tolerance' is very helpful to identify the probable mechanisms beyond sepsis-induced alterations of the immune system and their consequences, although it is not easily adaptable to humans, because it is an oversimplification of the far more complex concept of immunoparalysis seen in human sepsis.

The mechanisms underlining LPS tolerance are still ill-understood, though recently it has been hypothesised that sepsis-induced monocyte epigenetic reprogramming may play a pivotal role in the suppressive monocyte phenotype (Delano and Ward 2016). Alterated nuclear translocation of transduction molecules, decreased stability of messenger RNA for cytokine genes (Opal 2007), and enhanced expression of two micro-RNAs (miR146 e miR155) (Biswas and Lopez-Collazo 2009) are mechanisms implicated in the genetic reprogramming of immune cells.

Altogether, after LPS challenge, monocytes produce less levels of pro-inflammatory cytokine such as TNF-α, IL-1, IL-6, IL-12 and more anti-inflammatory ones. Moreover, the ability of monocytes to present antigens is highly impaired due to reduced expression of MCH II molecules such as HLA-DR (Biswas and Lopez-Collazo 2009; Delano and Ward 2016). It is noteworthy that not only monocytes, but also dendritic cells, neutrophils, T cells (Elyce 2011), and NK cells, are involved in the genesis of immunoparalysis (Delano and Ward 2016). The widespread apoptosis of specific subsets of immune cells may contribute as well (Opal 2007) (**Figure 1B**).

Therapeutical approach

Since the first attempt of anti-endotoxin treatment by Ziegler, published in 1982, several strategies aiming to remove endotoxin have been proposed, from agents that inhibit endotoxin synthesis, to anti endotoxin vaccines or anti endotoxin antibodies. Unfortunately, all of them have failed the U.S. Food and Drug Administration (FDA) clinical trials (Romaschin et al. 2012). Hence, recently much research on blood purification techniques able to remove LPS has been carried out, giving contrasting results. In the fourth edition of the Surviving Sepsis Campaign Guidelines (Rhodes et al. 2017), blood purification was considered for the first time, but neither recommended in favour nor against (Ilia et al. 2017).

Several cartridges for extracorporeal blood purification have been developed, though Toraymixin® has the highest removal capacities and is the most studied. Three large randomised controlled trials (RCT)s have been set up on Polymyxin-B (PMX-B) so far, giving contrasting results. The ABDOMIX trial did not demonstrate any benefit of PMX haemoperfusion in organ failure or mortality in patients with peritonitis-induced septic shock (Payen et al. 2015), while the *Early use of polymyxin B hemoperfusion in abdominal septic shock* (EUPHAS) trial, reported improvement in organ dysfunction, and reduction of 28-day of mortality (Cruz et al. 2009). Similar results were demonstrated in the retrospective EUPHAS 2 registry (Cutuli et al. 2016). Finally, *Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled trial of Adults Treated for Endotoxemia and Septic Shock* (EUPHRATES), a placebo-controlled multicentred blinded trial was concluded in 2016 (Klein et al. 2014). Currently, the only existing report is a press release that states that PMX haemoperfusion significantly improved 28-day survival outcomes of patients with an EAA level in the range of 0.6-0.9 and a multiple organ dysfunction > 9, based on the results of a subgroup analysis (spectraldx.com/assets/spectral-rls-05.30.17.pdf).

As described by De Grooth et al. (2018),

substantial between-trial heterogeneity limits the reproducibility and generalisability of septic shock research and may inhibit the discovery of beneficial therapies for specific (sub)-populations.

Conclusion

Sepsis and septic shock are still associated with a high mortality risk, and endotoxin is probably the most important trigger of inflammatory response. Although the complex interaction between the immune system and endotoxin has not been completely elucidated so far, it is clear that elevated endotoxaemia is associated with increased mortality and organ dysfunction in critically ill patients.

The clinical efficacy of extracorporeal blood purification techniques in sepsis and septic shock remains uncertain, even though Polymyxin B hemoperfusion could be considered as a complementary therapeutic strategy for unresponsive endotoxin-based septic shock. ■

Conflict of interest

Greta Giuliano and Gabriella Licitra declare that they have no conflicts of interest. Francesco Forfori received honoraria for lectures from Baxter, Orion, Pfizer, Biotest and Estor.

Abbreviations

ADP action potential duration
AKI acute kidney injury
ALI acute lung injury
DAMP damage-associated molecular pattern
EAA endotoxin activity assay
GFR glomerular filtration rate
ICU intensive care unit
LPS lipopolysaccharide
PAMP pathogen-associated molecular pattern
PRR pattern recognition receptor
RCT randomised controlled trial
REA reactive oxygen species
TLR toll-like receptor
TRIF toll-like receptor domain adaptor inducing interferon-β

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Fluids in shock

Fluid management during shock from physiology to bedside

Shock is a common life-threatening, generalised form of acute circulatory failure in critically ill patients, which is usually managed by infusing fluids to increase cardiac output and supply the systemic oxygen request. International guidelines recommend use of an aggressive fluid resuscitation in the early phases of shock. In this context, crystalloids, including balanced solutions, are suggested as first-line fluid therapy. However, a single physiological or biochemical measurement able to adequately assess the balance between cardiac output and perfusion pressure is still not available. Moreover, the haemodynamic targets and safety limits indicating whether or not to stop this treatment in already resuscitated patients are still undefined. A fluid should be considered as a drug and the intensivist should consider its pharmacodynamic and pharmacokinetic properties, and whether or not a patient is resistant to this therapy—before administration.

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Why administer fluids? From physiology to bedside

Shock is a life-threatening, generalised form of acute circulatory failure affecting one-third of intensive care unit (ICU) patients (Sakr et al. 2006; Cecconi et al. 2014). It is associated with the imbalance between the oxygen delivery (DO_2) provided by the cardiac function, and the systemic oxygen request. The first variable is defined as the product of oxygen content and the cardiac output (CO), whereas inadequate cellular oxygen utilisation derives from a tissue oxygen request exceeding the DO_2, or to the cellular inability of using O_2. This latter condition is due to mitochondrial dysfunction (Brealey et al. 2002) and deregulated cell-signalling pathways during sepsis-induced multiple organ damage (Singer 2017). A large trial regarding dopamine or norepinephrine infusion for shock reversal in more than 1600 ICU patients demonstrated that septic shock occurred in the vast majority of ICU patients (62%), while cardiogenic shock (16%), hypovolaemic shock (16%) and other types of distributive (4%) or obstructive (2%) shock are less frequent. Fluid infusion to correct haemodynamic instability is a key, early and common intervention in ICU patients with shock (Myburgh and Mythen 2013; Rhodes et al. 2017).

The technique of fluid resuscitation to treat an episode of shock was first described by Dr. Thomas Latta nearly 200 years ago in a letter to the editor of *The Lancet* (Latta 1832). He injected repeated small boluses of a fluid solution equivalent to approximately ½ Ringers lactate and observed the clinical changes of his first patient (an elderly woman). The first bolus did not have any visible effect, but after multiple boluses (overall 2.8 litres) "soon the sharpened features, and sunken eye, and fallen jaw, pale and cold, bearing the manifest imprint of death's signet, began to glow with returning animation; the pulse returned to the wrist." To give fluids during shock and observe the clinical improvement of the patient at bedside seemed reasonable in 1831 and still makes sense! In fact, optimal fluid management is a key component to improve the outcome of haemodynamically unstable ICU patients, since both hypovolaemia and hypervolaemia are harmful (Cecconi et al. 2014).

When to administer fluids? Triggers and safety limits of fluid administration

While consensus exists regarding the need for aggressive fluid resuscitation in the early phases of shock (Rhodes et al. 2017), the haemodynamic targets and the safety limits indicating whether or not to stop this treatment in already resuscitated patients are still undefined (Hjortrup et al. 2016; Rhodes et al. 2017). Moreover, a single physiological or biochemical measurement able to adequately assess the balance between the changes in heart function and in DO_2, peripheral perfusion pressure and O_2 request, is not available. Surely, giving fluids to increase the cardiac output (CO) and, as a consequence, DO_2, seems reasonable.

CO is the dependent variable of the physiological interaction of cardiac function (described by the observations of Otto Frank and Ernest Starling more than 100 years ago) and venous return function (based on Guyton's relationship between the elas-

tic recoil of venous capacitance vessels, the volume stretching the veins, the compliance of the veins and the resistance of the venous system). In this context, fluids should be used to increase CO only if the plateau of cardiac function is not reached. At this point, in fact, and probably even before reaching this point, fluid administration does not increase CO and can be considered as futile or even harmful.

However, clinical assessment of the Frank-Starling curve position of the ventricle is complex and the prediction of fluid responsiveness in ICU patients is still challenging (Monnet et al. 2016). The fluctuations of arterial waveform caused by the fixed and constant insufflations in patients undergoing a >8 ml/kg controlled mechanical ventilation have been successfully tested to predict fluid responsiveness (Monnet et al. 2016). However, most ICU patients are protectively ventilated or retain to some extent spontaneous breathing activity (McConville and Kress 2012; Esteban et al. 2013; Mahjoub et al. 2014), making the changes in intrathoracic pressure neither fixed nor constant and, in turn, the dynamic indexes unreliable (Monnet et al. 2016).

In daily practice hypotension is usually indicated as the bedside trigger to start fluid administration and the mean arterial pressure (MAP) is the physiological target indicating whether or not to continue fluid infusion for most ICU physicians (Cecconi et al. 2015). The assumption that hypotension and shock are synonymous is misleading. In fact, restoring MAP above predetermined targets does not necessarily mean reverting shock, whereas MAP below guidelines' predefined thresholds does not necessarily indicate shock (Cecconi et al. 2014). Unfortunately, the physiological relationship between changes in systemic pressures and stroke volume becomes weak in previously resuscitated ICU patients, especially during an episode of septic shock (Dufour et al. 2011; Pierrakos et al. 2012; Lakhal et al. 2013). For these reasons, the MAP target should be individualised to each patient, combining the assessment of blood lactates, mixed venous oxygen saturation and veno-arterial carbon dioxide difference (Cecconi et al. 2014). Finally, during fluid administration, the assessment of the changes of both right and left ventricle filling pressures is useful as a safety limit to guide further infusion. In fact, despite static indexes are not reliable in predicting fluid responsiveness, the increase of filling pressures suggests that the ventricle is operating on the flat part of the Frank-Starling's curve.

Table 1. Clinical bedside triggers of fluid administration

Variable	Pros	Cons
Mean arterial pressure	• Target indicated in the guidelines • Easy to measure and to monitor	• Difficult to be tailored in some categories of patients (hypertensive, chronic renal failure)
Lactate	• The reduction is usually associated with shock reversal • Easy to measure • Early variation even in normotensive patients	• Not specific under certain conditions (poisoning, liver failure, shivering)
Capillary refill time	• Easy and costless • Good correlation with systemic perfusion	• Low sensitivity and specificity in vasculopathic patients
Oliguria	• High sensitivity	• Difficult to evaluate in previous renal failure patients • Need a few hours for defining a trend • Affected by diuretics use
Mottled skin	• High specificity	• Not always present or late sign of hypoperfusion

> **"fluid infusion to correct haemodynamic instability is a key, early and common intervention in ICU patients with shock"**

How to administer fluids? Pharmacodynamic and pharmacokinetic of fluid administration

Fluids should be considered as a drug and, as a consequence, the ICU physician should assess whether or not a patient is resistant to this therapy—before administration. Unfortunately, the reliability in predicting fluid responsiveness and guiding fluid therapy of the physical bedside examination, chest radiography, central venous pressure and urine output (specifically in septic patients) is very limited (see **Table 1**).

An early fluid resuscitation with 30 ml/kg is suggested as the first-step approach to septic shock (Rhodes et al. 2017). On the one hand, a large initial fluid load seems suitable to revert acute hypovolaemia; on the other hand a tailored fluid therapy could prevent fluid overload after shock relapse (Hjortrup et al. 2016).

A modern approach to guide fluid therapy to revert an episode of haemodynamic instability should include a portioned fluid administration and bedside tests, aiming at revealing preload dependence. Repeated fluid challenges [(FCs); an infusion of small aliquots of 300 to 500 ml of fluid administered over 20-30 minutes, as indicated by the guidelines (Rhodes et al. 2017)] to assess fluid responsiveness should be preferred to a larger and continuous infusion of any fluid. Recent findings on postoperative patients suggest that the minimum volume required to perform an effective fluid challenge is 4 ml/kg infused over 5 minutes (Aya et al. 2015).

In principle, FCs should avoid or reduce ineffective fluid administration. However, the effect on haemodynamics should be only assessed by measuring the changes in CO. Recently, RACE (rapid assessment by cardiac echography) has been suggested as a first-line tool to evaluate the type of shock if the clinical examination does not lead to a clear diagnosis, even when used by a minimally trained intensivist (Cecconi et al. 2014; Finfer et al. 2018).

Table 2. Haemodynamic monitoring during shock

Variable	Pros	Cons
Echocardiography	• Prompt evaluation • Not invasive • Suggested as first-line haemodynamic evaluation after clinical examination • Rapid differentiation of the cause of shock	• Need learning curve for more precise measurements • Not yet available in all intensive care units • Operator/patient dependent • Not useful for continuous monitoring
Calibrated pulse contour methods	• Accurate in estimating cardiac output and trending cardiac function • Provide dynamic indexes of fluid responsiveness and also estimate systemic distribution of fluids	• Invasive and time-consuming • Not available in all intensive care units • Limited by cardiac arrhythmias or vascular abnormalities
Uncalibrated pulse contour methods	• Not or minimally invasive • Prompt measurement • Provide dynamic indexes of fluid responsiveness	• Questioned accuracy in critically ill patients • Not available in all intensive care units • Limited by cardiac arrhythmias or vascular abnormalities
Oesophageal Doppler	• Minimally invasive • Prompt measurement	• Contraindicated in those with oesophageal pathology • The acquisition of the optimal acoustic signal may require frequent repositioning • Difficult to use in awake patients

Despite the increasing number of haemodynamic tools measuring CO or its surrogates, continuous monitoring of cardiac function is far from being considered a standard in haemodynamically unstable ICU patients (Cecconi et al. 2015) (see **Table 2**). As a consequence, the outcome of a FC is often ambiguous in terms of haemodynamic response (responder/non-responder), leading to adjunctive and often futile fluid administration (Cecconi et al. 2015). Recently, a few studies evaluated the response to FC by considering the early variation of the stroke volume or dynamic indexes to a quick infusion of smaller portion of the entire FC (Marik 2015). On the other hand, the dose (ml/Kg) of a FC can also affect the percentage of responders to the test (Aya et al. 2015). In practice there is no standard way of performing a FC (Messina et al. 2017; Toscani et al. 2017). Studies investigating the different components (type of fluids, dose, speed and response) of a FC are largely awaited (Aya et al. 2017; Toscani et al. 2017; Bennett et al. 2018).

Finally, several haemodynamic tests have been proposed in the literature to evaluate the preload dependency of the right ventricle by increasing venous return before FC administration. Among them is the passive leg raising (PLR) test. PLR is performed by simultaneously lowering the trunk and raising the inferior limbs, changing the patient's position from semi-recumbent to a position in which the head and the trunk are horizontal and the legs are elevated at 45°(Monnet and Teboul 2015). This manoeuvre leads to an autotransfusion of about 300 ml of blood volume recruited from the capacitance veins of the legs and pushed to the heart; an increase in CO of about 10%-15% reliably predicts fluid responsiveness. Unfortunately, lower trunk trauma, increased intracranial pressure, low level of sedation and abdominal hypertension might limit PLR reliability.

> "the assumption that hypotension and shock are synonymous is misleading"

Which fluid in critically ill patients with shock?

The ideal fluid for patients in shock should have a composition as similar as possible to the extracellular fluid, to support cellular metabolism and avoid organ dysfunction, and should increase intravascular volume and persist over time, to optimise CO. Unfortunately, no ideal fluid exists, and the available fluid options are roughly divided in three groups: crystalloids, colloids, and blood products. The latter have few very specific indications including shock in trauma patients and haemorrhagic shock, and will not be discussed in this review (Stensballe et al. 2017).

Colloids are composed of large molecules designed to remain in the intravascular space for several hours, increasing plasma osmotic pressure and reducing the need for further fluids. Despite the theoretical advantages of this model, subsequent studies challenged this view in sepsis patients, where alterations in glycocalyx and endothelial permeability may lead to extravasation of colloid's large molecules (Brunkhorst et al. 2008), abolishing their primary advantage. Colloids are further divided into semi-synthetic colloids and albumin. The former includes hydroxyethyl starches, dextrans and gelatins and have demonstrated either no effect (Annane et al. 2013) or detrimental consequences in critically ill patients, increasing the risk of kidney injury (Myburgh et al. 2012; Perner et al. 2012) Thus, the use of semi-synthetic colloids in shock patients should be abandoned.

The role of albumin is still debated. While theoretically promising for its anti-inflammatory and anti-oxidant proprieties (Vincent 2009), and for its supposed longer intravascular confinement due to the interaction between its surface negative charges and endovascular glycocalyx (Vincent 2009), there is no clear evidence of its efficacy in critically ill patients (Finfer et al. 2004; Caironi et al. 2014). The use of albumin was associated with improved mean arterial pressure with an infusion of a lower volume, but the relative risk of mortality was similar to the crystalloid infusion (Caironi et al. 2014). A predefined subgroup analysis of the SAFE study suggested that the use of albumin should be avoided in patients with traumatic brain injury. Debate is still ongoing, and the safer indication for albumin use in shock patients is liver failure (Salerno et al. 2013).

On the other waterside of fluid therapy, crystalloids are composed of water and electrolytes.

Normal saline was the first crystalloid

solution to be used in humans. Its drawbacks are a very high concentration of chloride and high osmolarity, which were associated with nephrotoxicity and hyperchloraemic acidosis (Yunos et al. 2015). Several balanced solutions were later proposed, such as Ringer lactate (Hartman solution), Ringer acetate and PlasmaLyte. These solutions have *normal* chloride concentration, lower osmolarity (between 280 and 294) and are buffered with lactate or acetate to maintain fluid neutrality.

Two randomised studies were recently published to assess the effect of balanced solutions vs normal saline. The SPLIT trial, conducted in 4 ICUs, showed no advantage in either group (Young et al. 2015). The SMART trial was a monocentric study (5 ICUs/1 academic centre) and yielded similar results, with no difference in mortality or kidney injury using balanced solution vs normal saline (Semler et al. 2018). A significant difference in favour of PlasmaLyte was found in days free from renal replacement therapy and in a composite outcome of renal complications and mortality in the SMART trial (Semler et al. 2018). Both trials were cluster randomised, and negative trial results may also reflect the relatively small quantity of fluid infused in the two groups (median quantity less than 2 litres). Despite the lack of definitive evidence, balanced solutions have theoretical advantages that should be compared with the risk of hyperchloraemic acidosis after large volume resuscitation with normal saline. Consequently, balanced solutions are probably the best choice as a first-line fluid therapy in patients with shock.

Conclusions

Fluids are a crucial component of the resuscitation of patients in shock. A paradigm shift is taking place in fluid therapy, changing from the administration of large volume to a more targeted and personalised approach. Fluids should be considered as a drug, and should be administered after testing preload dependency and with continuous evaluation of preload dependency/CO response. Fluid therapy should be paired with timely monitoring of clinical and metabolic signs of shock. Despite the lack of definitive evidence, balanced crystalloids are the most promising fluids in patients in shock, while semi-synthetic colloids should be definitively avoided in this population. ■

Conflict of interest

Maurizio Cecconi is a consultant for Edwards Lifesciences, LiDCO and Cheetah Medical.

Abbreviations

CO cardiac output
FC fluid challenge
ICU intensive care unit
MAP mean arterial pressure

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/o1x

It is time for improved fluid stewardship

A conceptual framework for developing institutional programmes and guidelines to enhance fluid stewardship (especially in the intensive care unit [ICU] environment), an activity that includes appropriate selection, dosing, duration, de-escalation, and monitoring of fluid therapy.

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The primary goal of fluid stewardship is to optimise clinical outcomes while minimising unintended consequences of intravenous (IV) fluid administration. This article sets the stage for a conceptual framework for developing institutional programmes and guidelines to enhance fluid stewardship (especially in the ICU environment), an activity that includes appropriate selection, dosing, duration, de-escalation, and monitoring of fluid therapy. In patients with septic shock, haemodynamic stabilisation using fluids is a major challenge because clinicians are faced with many unresolved questions. It is clear that clinicians regard intravenous fluids like prescription drugs and should take into account the indications and contraindications (Perner et al. 2012; Van Regenmortel et al. 2014; Malbrain et al. 2012; Myburgh et al. 2012; Guidet et al. 2012; Annane et al. 2013), as they may affect patient-centred outcomes (Myburgh and Mythen 2013). Clinicians should also consider not only the risk of administering too little, but also too much fluid, as the deleterious consequences of fluid overload become better established (**Figure 1**).

1. Definitions

It is important to precisely define the various terms commonly used in the context of fluid management to describe fluid balance, fluid overload, different dynamic phases during fluid therapy, and different types of fluids; these definitions are partially based on published conceptual models (Van Regenmortel et al. 2013; Myburgh and Mythen 2013; Hoste et al. 2014; Vincent and De Backer 2013; Malbrain et al. 2014; Vincent and Pinsky 2018).

2. The four Ds of fluid therapy

Many clinicians consider specific aspects when dealing with antibiotics: different classes, spectrum, toxicity, dose, compounds. Likewise, prescription of intravenous fluids should proceed with the same caution, taking into account the compounds, pharmacodynamic and pharmacokinetic properties of different fluids. Another way of conceptualising this is considering the "four Ds" of fluid therapy when treating patients with septic shock: drug, dosing, duration, and de-escalation (**Table 1**) (Malbrain et al. 2015). Fluid misuse, like antibiotic misuse, almost certainly has severe consequences for the patient.

2.1. Drug

2.1.1. Inappropriate therapy

All resuscitation, replacement and even maintenance fluids can contribute to the formation of interstitial oedema, particularly in patients with systemic inflammation associated with altered endothelial function (Myburgh and Mythen 2013). For each type of fluid, there are distinct indications: crystalloids vs colloids; synthetic vs blood-derived; balanced vs unbalanced; intravenous vs oral.

Because of their potential risk, **hydroxyethyl starches** are contraindicated in patients with septic shock, burns, acute or chronic kidney injury, or oliguria not responsive to fluids (Rhodes et al. 2017).

Glucose water should never be used as resuscitation fluid. Surprisingly, **normal saline**, which does not contain potassium, will result in higher serum potassium levels in patients with renal impairment compared to a balanced solution (lactated Ringer's), which contains 5 mmol/L of potassium, due to concomitant metabolic acidosis secondary to a reduced strong ion difference (SID) (Khajavi et al. 2008; Langer et al. 2015). In an analogy to antibiotic treatment, where inappropriate therapy may result in more organ failure, longer ICU and hospital lengths of stay, longer duration of mechanical ventilation and higher mortality (Ibrahim et al. 2000; Hoffken and Niederman 2002), (ab) normal saline as resuscitation fluid should not be administered in large amounts, as it carries the risk of hypernatraemic hyperchloraemic metabolic acidosis, acute kidney injury (AKI) and possible RRT (renal replacement therapy), and mortality (Semler et al. 2018).

2.1.2. Appropriate therapy

Patient risk factors (prior antibiotic use, duration of mechanical ventilation, co-morbidity, hospital length of stay above 5 days, corticosteroids, recent hospitalisation, residence in nursing home,…)

play important roles in the appropriate choice of empiric antibiotics (Kollef et al. 2006). Similarly, patient risk factors (fluid balance, fluid overload, capillary leak, acid-base status, co-morbidity, kidney function, organ function) also play an important role in empiric fluid therapy.

In patients with hypoalbuminaemia and septic shock, **albumin** may be an appropriate resuscitation fluid, especially in the late phase after the initial resuscitation (Rhodes et al. 2016; Caironi et al. 2014).

2.1.3. Combination therapy

Possible benefits of antibiotic combination therapy include: broader spectrum, synergy, avoidance of emergence of resistance, less toxicity,…(Tamma et al. 2012). Possible benefits of fluid combination therapy include: specific fluids for different indications (replacement vs maintenance vs resuscitation), and less toxicity.

2.1.4. Class

With respect to antibiotic administration, it is important to consider broad-spectrum vs specific narrower coverage classes. The choice of the antibiotic has a real impact on efficacy and toxicity. Likewise, hypotonic or hypertonic fluids, with high or low sodium or chloride level, lactate or bicarbonate buffer, glucose or not, are all equally important aspects of fluid therapy. This will have a direct impact on acid-base equilibrium, cellular hydration and electrolyte regulation.

2.1.5. Appropriate timing

Survival decreases 7% with each hour delay of antibiotic administration in patients with septic shock (Kumar et al. 2006). In refractory shock early fluid resuscitation has been proven beneficial in previous studies (Rivers et al. 2001). The longer the delay in fluid administration, the more microcirculatory hypoperfusion and subsequent organ damage (related to ischaemia reperfusion injury). Murphy et al. compared outcomes related to early adequate vs early conservative and late conservative vs late liberal fluid administration and found that the combination of early adequate and late conservative fluid management carried the best prognosis (Murphy et al. 2009).

2.2. Dosing

2.2.1. Poison

As Paracelsus nicely stated: "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous." It is the dose that makes the antibiotic poisonous, and the same holds true when it comes to fluid management in the critically ill. The risk of excessive fluid administration leading to an increase in the cumulative fluid balance has been clearly demonstrated (Malbrain et al. 2014), especially in critically ill patients with septic shock (Vincent et al. 2006) and/or acute respiratory distress syndrome (Jozwiak et al. 2013). Maintenance fluids should be used cautiously and only to cover daily needs when the patient receives no other oral or intravenous fluid intake. Their prescription should take other sources of fluids and electrolytes into account. Therefore when a patient already receives daily needs of water, glucose and electrolytes via other means (enteral or parenteral nutrition,

Table 1. Analogy between the 4 Ds of antibiotic and fluid therapy

Description	Terminology	Antibiotics	Fluids
Drug	*Inappropriate therapy*	More organ failure, longer ICU LOS, longer hospital LOS, longer MV	Hyperchloraemic metabolic acidosis, more AKI, more RRT, increased mortality
	Appropriate therapy	Key factor in empiric AB selection is consideration of patient risk factors (e.g. prior AB, duration MV, corticosteroids, recent hospitalisation, residence in nursing home)	Key factor in empiric fluid therapy is consideration of patient risk factors (e.g. fluid balance, fluid overload, capillary leak, kidney and other organ function). Don't use glucose as resuscitation fluid
	Combination therapy	Possible benefits: e.g. broader spectrum, synergy, avoidance of emergence of resistance, less toxicity	Possible benefits: e.g. specific fluids for different indications (replacement vs maintenance vs resuscitation), less toxicity
	Class	Broad-spectrum or specific, Beta-lactam or glycopeptide, additional compounds as tazobactam. The choice has a real impact on efficacy and toxicity	Hypo- or hypertonic, high or low chloride and sodium level, lactate or bicarbonate buffer, glucose containing or not. This will impact directly acid-base equilibrium, cellular hydration and electrolyte regulation
	Appropriate timing	Survival decreases with 7% per hour delay. Needs discipline and practical organisation	In refractory shock, the longer the delay the more microcirculatory hypoperfusion
Dosing	*Pharmacokinetics*	Depends on distribution volume, clearance (kidney and liver function), albumin level, tissue penetration	Depends on type of fluid: glucose 10%, crystalloids 25%, vs colloids 100% IV after 1 hour, depends on distribution volume, osmolality, oncoticity, kidney function
	Pharmacodynamics	Reflected by the minimal inhibitory concentration. Reflected by "kill" characteristics, time (T>MIC) vs concentration (Cmax/MIC) dependent	Depends on type of fluid and desired location: IV (resuscitation), IS vs IC (cellular dehydration)
	Toxicity	Some AB are toxic to kidneys, advice on dose adjustment needed. However, not getting infection under control isn't helping the kidney either	Some fluids (HES) are toxic for the kidneys. However, not getting shock under control is not helping the kidney either
Duration	*Appropriate duration*	No strong evidence but trend towards shorter duration. Don't use AB to treat fever, CRP, or chest x-ray infiltrates but use AB to treat infections	No strong evidence but trend towards shorter duration. Don't use fluids to treat low CVP, MAP, or UO, but use fluids to treat shock
	Treat to response	Stop AB when signs and symptoms of active infection resolve. Future role for biomarkers (PCT)	Fluids can be stopped when shock resolves (normal lactate). Future role for biomarkers (NGAL, cystatin C, citrullin, L-FABP)
De-escalation	*Monitoring*	Take cultures first, choose empiric AB and tailor when information becomes available	After stabilisation with EAFM (normal PPV, normal CO, normal lactate) stop ongoing resuscitation and move to LCFM and LGFR (=desuscitation)

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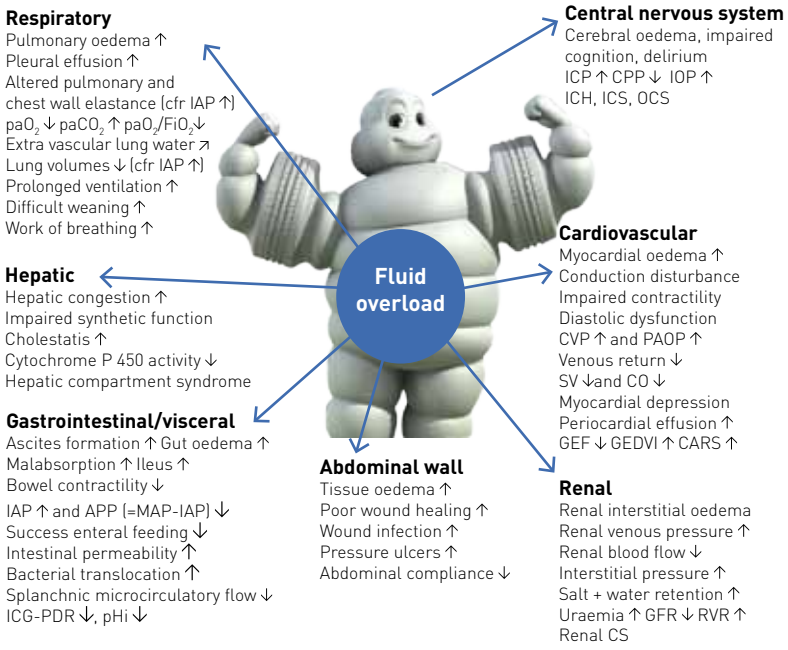
AB antibiotic AKI acute kidney injury Cmax maximal peak concentration CO cardiac output CRP C reactive protein CVP central venous pressure EAFM early adequate fluid management EGDT early goal-directed therapy IC intracellular ICU intensive care unit IS interstitial IV intravascular LCFM late conservative fluid management L-FABP L-type fatty acid binding protein LGFR late goal directed fluid removal LOS length of stay MAP mean arterial pressure MIC mean inhibitory concentration MV mechanical ventilation NGAL neutrophil gelatinase-associated lipocalin PCT procalcitonin PPV pulse pressure variation RRT renal replacement therapy UO urine output



APP: abdominal perfusion pressure IAP: intra-abdominal pressure IAH: intra-abdominal hypertension ACS: abdominal compartment syndrome CARS: cardio-abdominal-renal syndrome CO: cardiac output CPP: cerebral perfusion pressure CS: compartment syndrome CVP: central venous pressure GEDVI: global end diastolic volume index GEF: global ejection fraction GFR: glomerular filtration rate ICG-PDR: indocyanine green plasma disappearance rate ICH: intracranial hypertension ICP: intracranial pressure ICS: intracranial compartment syndrome IOP: intra-ocular pressure MAP: mean arterial pressure OCS: ocular compartment syndrome PAOP: pulmonary artery occlusion pressure pHi: gastric tonometry RVR: renal vascular resistance SV: stroke volume

medication solutions,…) specific maintenance fluids must be stopped.

2.2.2. Pharmacokinetics

The principle of pharmacokinetics is very well known during antibiotic administration. Pharmacokinetics (PK) describes how the body affects a drug, resulting in a particular plasma and effect site concentration (Elbers et al. 2015). PK depends on distribution volume, clearance (kidney and liver function), tissue penetration and in some situations also on albumin levels. Increased distribution volume is seen with capillary leak, hypo-oncotic states, extracorporeal circuits, surgical drains, large burns and mechanical ventilation. Pharmacokinetics of intravenous fluids depends on distribution volume, osmolality, tonicity, oncoticity and kidney function. Eventually, the half time depends on the type of fluid, but also on the patient's condition and the clinical context. Volume kinetics is an adaptation of pharmacokinetic theory that makes it possible to analyse and simulate the distribution and elimination of intravenous fluids (Hahn 2010). The context-sensitive half-time of crystalloids and colloids may change and vary over time depending on the patient's condition. As long as crystalloids or colloids are infused they will exert a similar volume expansion effect and their **distribution** and/or **elimination** and excretion will be slowed in cases of shock, renal failure, sedation, or general anaesthesia (Hahn 2010; 2014). This may explain why crystalloids have a much better short-term effect on the plasma volume than previously believed. Their efficiency (i.e. the plasma volume expansion divided by the infused volume) is 50-80% as long as **infusion** continues, and even increases to 100% when the arterial pressure has dropped. Elimination is very slow during surgery, and amounts to only 10% of that recorded in conscious volunteers.

2.2.3. Pharmacodynamics

Pharmacodynamics (PD) relates plasma concentrations to a specific effect, i.e. how the antibiotic affects the body and the bacteria. As previously described, antibiotic plasma concentrations are determined by dosing strategy, volume of distribution (Vd) and clearance (CL) (Elbers et al. 2015). Volume dynamics depends on the type of fluid used and desired location: intravascular (resuscitation), interstitial vs intracellular (cellular dehydration). Volume kinetics and dynamics depend on underlying conditions.

2.3. Duration

2.3.1. Appropriate duration

The duration of fluid therapy is equally important and the volume must be tapered when shock is resolved. However, many clinicians use certain triggers to start, but are less aware of triggers to stop fluid resuscitation, hence carrying the potential of fluid overload and all its detriments (Malbrain et al. 2014; Benes et al. 2015). As with duration of antibiotics, there is no strong evidence but a trend towards benefit from shorter duration of IV fluids (Hjortrup et al. 2016). Clinicians should not use fluids to treat low central venous pressure, mean arterial pressure, or urine output per se, but to treat shock instead. For fluids, the Frank-Starling relationship between cardiac output and cardiac preload is the equivalent of the dose effect curve for standard medications. Because of the shape of the Frank-Starling relationship, the response of cardiac output to the fluid-induced increase in cardiac preload is not constant (Monnet et al. 2017).

2.3.2. Treat to response

Clinicians should stop antibiotics when signs and symptoms of active infection resolve. Likewise, fluids should be stopped when shock is resolved (e.g. normal lactate). As with antibiotics (e.g. CRP or procalcitonin), the future role for biomarkers (e.g. neutrophil gelatinase-associated lipocalin, cystatin C, citrullin, or liver-type fatty acid binding protein) needs to be established. After the very initial fluid administration, only one half of patients with circulatory failure respond to continued intravenous fluid administration with an increase in cardiac output (Bentzer et al. 2016).

2.4. De-escalation

2.4.1. Withholding or withdrawing

The final step in fluid therapy is to consider withholding or withdrawing resuscitation fluids when they are no longer required (Malbrain et al. 2014; Benes et al. 2015; O'Connor and Prowle 2015). Along with conditioning fluid administration on the presence of fluid responsiveness, this contributes to reducing overall cumulative fluid balance. A positive cumulative fluid balance should be avoided by all means as studies have shown that fluid overload is an independent predictor for increased morbidity and mortality (Malbrain et al. 2014; Silversides et al. 2017). Eventually, active fluid removal may be indicated in some patients with global increased permeability syndrome (GIPS) and volume overload, and this is referred to as de-resuscitation. As

Table 2. The ROSE concept avoiding fluid overload

	Resuscitation	Optimisation	Stabilisation	Evacuation
Hit sequence	First hit	Second hit	Second hit	Third hit
Time frame	Minutes	Hours	Days	Days to weeks
Underlying mechanism	Inflammatory insult	Ischaemia and reperfusion	Ischaemia and reperfusion	Global Increased Permeability Syndrome
Clinical presentation	Severe shock	Unstable shock	Absence of shock or threat of shock	Recovery from shock, possible Global Increased Permeability Syndrome
Goal	Early adequate goal-directed fluid management	Focus on organ support and maintaining tissue perfusion	Late conservative fluid management	Late goal-directed fluid removal (de-resuscitation)
Fluid therapy	Early administration with fluid boluses, guided by indices of fluid responsiveness	Fluid boluses guided by fluid responsiveness indices and indices of the risk of fluid administration	Only for normal maintenance and replacement	Reversal of the positive fluid balance, either spontaneous or active
Fluid balance	Positive	Neutral	Neutral to negative	Negative
Primary result of treatment	Salvage or patient rescue	Organ rescue	Organ support (homeostasis)	Organ recovery
Main risk	Insufficient resuscitation	Insufficient resuscitation and fluid overload (e.g. pulmonary oedema, intra-abdominal hypertension)	Fluid overload (e.g. pulmonary oedema, intra-abdominal hypertension)	Excessive fluid removal, possibly inducing hypotension, hypoperfusion, and a "fourth hit"

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for antibiotics (**Table 1**), the duration of fluid therapy must be as short as possible, and the volume (i.e. dose) must be the lowest amount effective in treating shock.

2.4.2. Monitoring

While antibiotic de-escalation may not help individual patients, it could benefit the ICU as a whole by reducing the selection pressure for resistance. Similarly, after stabilisation (normal pulse pressure variation, normal cardiac output, normal lactate) clinicians need to stop ongoing (futile) fluid resuscitation and move to de-escalation (late conservative fluid management) and de-resuscitation (late goal-directed fluid removal) (see **Table 2** for explanation). However, too aggressive de-resuscitation may result in new hypoperfusion and increase in end-organ damage.

3. The four phases of fluid therapy

Recently a conceptual model of septic shock was proposed with four distinct dynamic phases of fluid therapy (Cordemans et al. 2012; Malbrain et al. 2018): **R**esuscitation, **O**ptimisation, **S**tabilisation, and **E**vacuation (de-resuscitation) (R.O.S.E.) (**Table 2**). Specifics of the four phases are: "When to start intravenous fluids?", "When to stop intravenous fluids?", "When to start de-resuscitation or active fluid removal?" and finally "When to stop de-resuscitation?"

4. Fluid stewardship

4.1. Conceptual framework

The multifaceted nature of fluid stewardship will need collaboration between different disciplines such as emergency medicine, critical care, anaesthesiology, nephrology, as well as general medicine, surgery and clinical pharmacy (Malbrain et al. 2018; Dellit et al. 2007). If the primary goal of fluid stewardship is to optimise clinical outcomes while minimising unintended consequences as detailed above, then the bedside clinician needs to understand fluid physiology. The combination of effective fluid stewardship with a comprehensive fluid bundle and organ function monitoring programme should limit the deleterious effects of inappropriate fluid prescription.

The specific IV fluid need depends on the indication: whether it is intended to replace lost fluids, maintain basic metabolic needs or restore circulating volume (Malbrain et al. 2018). To determine the right type of fluid therapy for the individual patient, the clinician must choose based on the clinical exam, laboratory results and the characteristics of the available IV fluids. Though commonly prescribed, intravenous fluids are not always appropriate (Gao et al. 2015). Prescription of intravenous fluids is often done by junior doctors using either an experience-based approach, or by habit, with limited input from senior colleagues (McCrory et al. 2017; Lobo et al. 2001; Lewis et al. 2014). A multidisciplinary collaboration is an alternative approach, as has been described for antibiotic stewardship (MacDougall and Polk 2005; Paterson 2006; Doron and Davidson 2011; Schuts et al. 2016).

A comparable strategy could be used for IV fluids, by implementing '**fluid stewardship**'. There is no clear definition yet, but one preliminary example could be "a series of coordinated interventions, introduced to select the optimal fluid, dose and duration of therapy that results in the best clinical outcome, prevention of adverse events and cost reduction" (Dellit et al. 2007; Goff 2011). Similar to antibiotic stewardship, the purpose is threefold. First, the most appropriate, individualised therapy has to be chosen. It is crucial that the right fluid is prescribed in the right dose and duration and that there is a timely evaluation to start de-escalating fluid therapy (Malbrain et al. 2018). Second, early detection and prevention of inappropriate fluid administration is necessary to avoid adverse events (Bates et al. 1995). Finally, cost containment should be achieved through implementation of preventive quality improvement measures (Etchells et al. 2012).

4.2. Assessment

First, measure baseline fluid dosing, duration, costs and use patterns; second, study indications for fluid administration (resuscitation, maintenance, replacement, nutrition); and finally, identify clinician indications for prescriptions.

4.3. Goals of desirable fluid use

Goals need to be formulated and 'appropriate', and rational IV fluid use needs to be defined for the institution and individual patients. Empiric versus goal-directed IV fluid treatment needs to be defined for the four indications (resuscitation, maintenance, replacement, nutrition). Treatment guidelines for clinical syndromes need to be established. The appropriateness of IV fluid therapy should be assessed during the audit process. Therefore, the process of an IV fluid treatment is divided into four stages (**Table 3**), based on an audit framework developed by the UK National Institute for Health and Care Excellence (NICE) (Sansom and Duggleby 2014; Padhi et al. 2013).

First, the physician has to assess the patient's IV fluid needs and decide on the right treatment (indication). Only the three major indications

need to be examined thoroughly for the purpose of a clinical audit: resuscitation, maintenance and replacement or redistribution. Second, every IV fluid prescription has to be detailed in order to ensure a proper administration and a fluid management plan is available to enable continuity of care. Third, the information in the hospital's fluid guideline or bundle is used to create different quality standards. Finally, these standards represent the necessary elements to do a full and qualitative check of appropriateness (see **Table 3**). If all standards are met, the therapy will be classified as appropriate for that patient.

4.4. Interventions on IV fluid prescribing

IV fluid prescribing consists of numerous elements. The day-to-day work of the core fluid stewardship members is to screen patients' medical records for appropriateness of IV fluid administration.

Further tasks may lie in the automatic review of the medical record after empiric use, fluid balance results, other laboratory data (urea and electrolytes, kidney function, albumin levels,…), and to provide advice on appropriate duration of fluid therapy. Finally, the fluid stewardship team could write an annual report to the hospital administration with calculation of clinical benefits and cost savings, if any.

4.5. Provide feedback, continuing education

The fluid stewardship team should organise a survey to test the prescriber's knowledge about composition of fluids, indications and monitoring of fluid status. The team can provide targeted education about particular fluid composition, or one specific fluid at a time, as well as empiric versus goal-directed treatment.

4.6. Implement Fluid Stewardship

Analagous to antibiotic practice in critically ill patients, it is time to introduce **fluid stewardship** in the ICU, through a few simple steps. Start with a snapshot: First, check what intravenous fluids are commonly used and for what indications. Next, perform a survey of knowledge (of the nurses, doctors, pharmacists, etc). Finally, perform a clinical audit of patient records (surgical vs medical). This should be followed by a **Plan-Do-Check-Act** (PDCA) cycle: set up guidance (introduce fluid bundle); perform education (including tailored lectures to all junior doctors) and ward-based opportunistic teaching; and regularly re-evaluate the situation and keep increased awareness (with flyers, screen-savers, etc.).

Table 3. Four stages of evaluation of IV fluid therapy

Stage of evaluation	*Audit standard*
1. Assessment	• Patient fluid balance is assessed on admission in the hospital • Patient's fluid and electrolyte needs are assessed as part of every ward review • Assessment includes the use of an appropriate clinical parameter for evaluation of the fluid balance • Recent lab result with urea and electrolytes (within 24 hours of fluid prescription)
2. Indication	A) RESUSCITATION • For patients in need of fluid resuscitation: o the cause of the fluid deficit is identified o an assessment of shock or hypoperfusion is made o a fluid bolus of 500mL of crystalloids is given • Patients who have received initial fluid resuscitation are reassessed • Care is upgraded in patients who have already been given >2000mL of crystalloids and still need fluid resuscitation after reassessment • Patients who have not had >2000mL of crystalloids and who still need fluid resuscitation after reassessment receive 250–500 mL of crystalloids and have a further reassessment B) MAINTENANCE • Patients should be assessed for maintenance IV fluids needs at least daily • If patients need IV fluids for routine maintenance alone, the initial prescription is restricted to: o 25–30 mL/kg/day (1 mL/kg/hr) of water and o approximately 1 mmol/kg/day of potassium (K+) and o approximately 1-1.5 mmol/kg/day of sodium (Na+) and o approximately 1 mmol/kg/day of chloride and o approximately 50–100 g/day (1-1.5 g/kg/day) of glucose to limit starvation ketosis • Definition of inappropriateness in case of electrolyte disturbances o Solutions not containing adequate amount of sodium in case of hyponatraemia (Na < 135 mmol/L) o Solutions not containing adequate amount of potassium in case of hypokalaemia K < 3.5 mmol/L) o Solutions containing too much sodium in case of hypernatraemia (Na > 145 mmol/L) o Solutions containing too much potassium in case of hyperkalaemia (K > 5 mmol/L) C) REPLACEMENT AND REDISTRIBUTION • If patients have ongoing abnormal losses or a complex redistribution problem, the fluid therapy is adjusted for all other sources of fluid and electrolyte losses (e.g. normal saline may be indicated in patients with metabolic alkalosis due to gastro-intestinal losses)
3. Prescription	• The following information is included in the IV fluid prescription: o the type of fluid o the rate of fluid infusion o the volume of fluid • The IV fluid prescription is adapted to current electrolyte disorders and other sources of fluid administration
4. Management	• Patients have an IV fluid management plan, including a fluid and electrolyte prescription plan over the next 24 hours • The prescription for a maintenance IV fluid is evaluated at least every 24 hours and changes after a clinical exam, a change in dietary intake or evaluation of laboratory results

Conclusions

There are only four major **indications** for fluid administration in the critically ill: resuscitation, maintenance, replacement and nutrition (enteral or parenteral).

In this review, a conceptual framework is presented looking at fluids as drugs by taking into account the four **D**s (**d**rug selection, **d**ose, **d**uration and **d**e-escalation) and the four phases of fluid therapy within the ROSE concept (resuscitation, optimisation, stabilisation, evacuation). This framework will provide answers to the four basic questions surrounding fluid therapy: 1) when to start IV fluids?; 2) when to stop fluid administration?; 3) when to start fluid removal and finally 4) when to stop fluid removal? Answering these **questions** for each patient can provide the basis for fluid stewardship (like antibiotic stewardship) in the ICU. This **fluid stewardship** can be promulgated through a three-pronged attack for fluid safety: namely educating, changing prescribing habits, and increasing awareness. Good luck! ■

For conflict of interest statement and full references see https://iii.hm/o1y

Abbreviations

ICU intensive care unit
IV intravenous

Nestlé Health Science
Satellite symposiums

The expanding *boundaries* of ICU nutrition

Monday 22nd October
12:30-14:00 | Room Vienna, level 2
Chair: Todd Rice & Carole Ichai

Speakers & Talks:

- *What did we learn from nutritional monitoring?*
  Stephan Jakob, Bern, Switzerland
- *The DIVINE nutritional management in ICU.*
  Todd Rice, Nashville, USA
- *The metabolic phenotype of skeletal muscle during early critical illness.*
  Nicholas Hart, London, UK
- *Metabolomics of Cell stress in Sepsis.*
  Kenneth Christopher, Boston, USA

Treatment of *dysphagia* in mechanically ventilated patients

Tuesday 23rd October
12:30-14:00 | Room Vienna, level 2
Chair: Giuseppe Citerio & Carole Ichai

Speakers & Talks:

- *Introduction & ESICM Dysphagia Survey results.*
  Giuseppe Citerio, Monza, Italy
- *Dysphagia in Mechanically Ventilated Patients: DYnAMICS results.*
  Jörg Schefold, Bern, Switzerland
- *Treatment of dysphagia in tracheostomized patients: PHAST-TRACT results.*
  Rainer Dziewas, Münster, Germany
- *Pharyngeal electrical stimulation in intubated patients.*
  Rudolf Likar, Klagenfurt, Austria

Nurses session

Nutritional support in the *critically* ill patient

Tuesday 23rd October
12:40-13:40 | Arena
Chair: Todd Rice & Carole Boulanger

Speakers & Talks:

- *How do I feed my obese patient? Results of new clinical trial.*
  Todd Rice, Nashville, USA
- *What do I need to consider in my feeding goals?*
  Michael Casaer, Leuven, Belgium
- *How can we improve our nutritional practice in the ICU?*
  Michael Hiesmayr, Vienna, Austria

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Vasoactive medication and RCTs: an impossible marriage

A review and introduction of the concept "enough"

We provide a brief overview of important physiology and the pharmacology of vasoactive drugs that are currently used in the ICU as well as newer agents, along with a concise review of recent publications comparing these agents. We attempt to answer the question what drug dose should be administered as well as what haemodynamic values to pursue, and how much fluids must be infused by introducing the concept of "enough".

Vasoactive medication is one of the cornerstones in the treatment of critically ill patients in shock. Shock can be defined as a failure of the circulatory system to provide adequate tissue perfusion resulting in cellular injury and organ failure. The definitive treatment of any type of shock is treatment of the underlying disease and in the case of sepsis achieving source control. This means that during treatment of critically ill patients, use of vasoactive drugs is part of a multi-approach and complicated but coherent and concerted treatment plan. The most important contribution of vasoactive medication is the help for immediate restoration of sufficient cardiovascular circulation to buy time for further treatment. This means that even if you give the best possible vasoactive drug, the patient will still die if the rest of the treatment is insufficient. Part of the other treatment in critically ill patients consists generally speaking of fluid resuscitation, giving the right antibiotic at the right dose, mechanical ventilation, and specific underlying disease-related treatment that can be medical and/or surgical. Other issues such as specific nursing care, decubitus prevention, feeding, early start of activity, timely weaning of the ventilator, prevention of errors and complications, doing all the things right, etc. play an undeniable role in patient survival.

Vasoactive medication is generally discussed and studied apart from other elements of treatment and the effect on the cardiovascular circulation is considered pivotal. This is in fact odd, since the (short-term) cardiovascular circulatory status will depend on many other factors, such as fluid resuscitation and importantly, mechanical ventilation. Another issue is the significant inter-individual variation in terms of desirable cardiovascular parameters, which can also change for one individual over the short and long term. In general in published studies haemodynamic goals are given in terms of specific figures. Now where a specific figure of blood pressure at one moment may be good in one patient, it might be too low for another patient (e.g. in case of pre-existent hypertension) and higher than needed (for good organ function) for another patient. And since all vasoactive drugs have side-effects that are generally dose-dependent, if a patient receives a higher dose than required, the patient is more exposed to side-effects than the benefit of the given drug would justify. Therefore we introduce the goal of "enough" for different cardiovascular parameters. Enough is defined as: not too low and not too high for a specific patient. For example, the best cardiac output for a patient is "enough," the best blood pressure and heart rate is also "enough." The only missing link is then to define "enough" for each particular patient. Thinking this way would avoid designing a study where a mean blood pressure of 70 mmHg would be compared with 80 mmHg, or a study where different doses of a vasoactive drug are given to establish prefixed haemodynamic parameters to patients in order to compare the vasoactive drugs (DeBacker et al. 2010; Russell et al. 2008; Asfar et al. 2014). As will be explained this approach will also hold for the desirable amount of fluid resuscitation: enough. In order to be able to estimate at the bedside what is enough for a particular patient, knowledge and understanding of basic physiology and pharmacology is required.

Basic issues

The pump generating the circulation of blood is placed in the thorax, where pressures vary according to the respiratory cycle, and the pump, a pressure chamber, is therefore placed in another pressure chamber. In normal conditions with spontaneous ventilation the intrathoracic pressure will lower during inspiration and return to normal pressure, which is slightly less than the atmospheric pressure. However, during mechanical ventilation the intrathoracic pressure, referring to the intrapleural pressure, is increased during inspiration and lowers, but remains above zero depending on the amount of PEEP (positive

end-expiratory pressure) during expiration. Since blood flow is from areas with a higher pressure to a lower pressure, the intrathoracic pressure determines the pressure gradient for blood streaming towards the heart. It is of note that the most important task of the heart is to pump and transfer the amount of blood that is presented at the right side of the heart. Therefore, cardiac output is determined by the flow that is presented at the heart, and the venous flow that enters the heart equals the cardiac output. Similarly, the amount of volume expelled by the right side of the heart—through the pulmonary circulation—equals the volume that is presented to the left side of the heart and is subsequently expelled by the left ventricle. Because of this it is important for the practising intensivist to acknowledge that—as put forward by Guyton—the venous return is determined by the pressure gradient between the peripheral veins and the right heart, i.e. the right atrium or CVP. In a formula, including the venous resistance:

$VR = (P_{ms}-P_{ra})/\text{venous resistance}$

Where VR = venous return, P_{ms} = mean systemic pressure, P_{ra} = right atrial pressure (**Figure 1**).

The venous system can be filled until the intravascular pressure starts to increase: this volume capacitance is called "unstressed volume." With further filling the veins will be stretched and the intravascular pressure will increase: the capacitance of this further filling volume is called "stressed volume." This theoretical model is depicted in **Figure 2**. When a fluid bolus increases the stressed volume, the driving force to the right atrium, right arterial pressure (RAP), can be increased, provided that the RAP will not increase accordingly. It is of note that with large volume resuscitation RAP may increase more than Pms, related to the reduced diastolic compliance of the heart and pericardium, resulting in a reduction of pressure difference P_{ms}-P_{ra} (Applegate et al. 1992).

Increasing intrathoracic pressure as seen in mechanical ventilation will reduce VR. On the other hand increased intrathoracic pressure will reduce afterload for the left ventricle. The effect of mechanical ventilation and lung volume on right ventricle afterload may vary according to the balance of stretching the extra-alveolar and intra-alveolar blood vessels: therefore increasing lung volume by

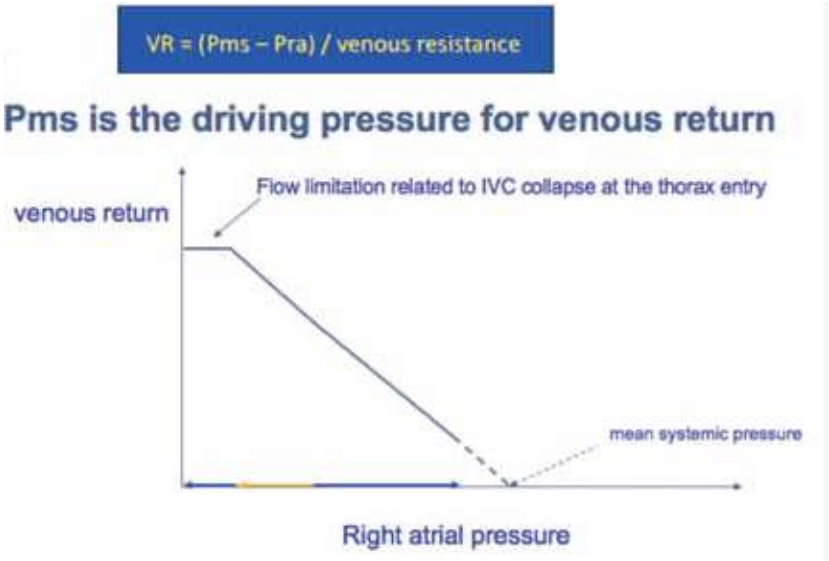

Figure 1. Relation between venous return and right atrial pressure

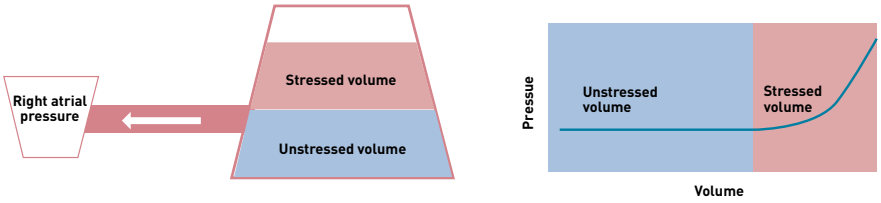

Figure 2. Theoretical model of stressed and unstressed (venous) volume, making clear that an unstressed volume is required first after which additional volume loading will increase right atrial pressure

e.g. PEEP may both lead to an increase and decrease of pulmonary vascular resistance (PVR) (Canada et al. 1982). Hyperinflation of the lung will result in overstretching of the alveolar vessels, thereby increasing PVR which can induce (acute) right ventricular failure. Hyperinflation can be the result of increased respiratory rate, larger tidal volumes (Vt) and insufficient expiratory time. Other heart-lung interactions, such as mechanical effects on the heart, and specific effects of sepsis on the heart and circulation are beyond the scope of this paper and can be read elsewhere (Marik and Bellomo 2016; Pinsky 2016; Fessler 1997). The situation and properties of the heart may even be more particular in case of previous coronary or hypertensive disease, with a huge spectrum of changes and severity.

In this context fluid responsiveness is frequently mentioned and an increase in stroke volume (SV) of 10-15% after a fluid challenge is considered as fluid responsiveness. The increase of myocardial contraction as a result of the stretching of actin and myosin muscular filaments (mostly indicated as according to the Frank-Starling principle) is in terms of energy consumption and demands a very favourable response of the heart. However, if the heart does not respond with an increase of SV to a fluid load, the latter might be harmful due to induction of oedema, which in turn may cause all kind of unfavourable effects for diverse organ functions (Hilton and Bellomo 2012). A recent meta-analysis of haemodynamically unstable patients showed that 50% remain fluid responsive after the initial resuscitation (Bentzer et al. 2016). Predictors for a positive fluid response are the passive leg raise test and pulse pressure variation (Bentzer et al. 2016). In terms of clinical parameters this has been translated in pulmonary and peripheral oedema, abdominal compartment syndrome, kidney injury and longer mechanical ventilation (Malbrain et al. 2014). Not surprisingly, there is an increasing focus on potential adverse effects caused by (too much) intravenous fluid resuscitation and this underscores that one should give

just enough to a patient. This perception has contributed to a shift of earlier use of vasoactive drugs to obtain haemodynamic goals in patients and to use less fluids.

From the previous it may become clear that execution of mechanical ventilation and fluid resuscitation, timely treatment of underlying disease as well as the intrinsic properties of the heart at a particular moment will influence the effect of any vasoactive drug. It is therefore extremely surprising that trials evaluating vasoactive drugs do not take mechanical ventilation and specific properties that are known to be of importance, into account.

Markers of "enough"

Although many studies, including randomised clinical trials (RCTs), focus on a single parameter (e.g. plasma lactate levels, SvO_2, cardiac output), clinicians use several parameters simultaneously to assess the situation and possible improvement of the condition of a patient. These parameters include signs of adequate organ function and perfusion: mental state, peripheral skin perfusion as determined by nose or knee temperature and mottled skin, capillary refill, diuresis, SvO_2, lactate levels, oxygenation, blood pressure, ECG abnormalities, venous curves on the monitor, cardiac output if measured. The experienced clinician will very much focus on pattern recognition of all these simultaneously assessed parameters. The response to any intervention will help to estimate whether the chosen therapy is favourable or not. The experienced clinician will furthermore use all available data and will not be guided by one single parameter alone, e.g. focus only on cardiac output. Errors as made in the past, such as striving for "supranormal" oxygen delivery (DO_2) with excessive fluid administration and very high doses of inotropes or very strict regulation of serum glucose levels with very high doses of insulin and at the price of causing hypoglycaemia, should now turn the intensivist into a physician who realises that just enough is enough and better is the enemy of good (Voltaire). Translated in an example: if a patient is hypotensive, anuric and confused, and responds to two times 250 mL of Ringers lactate intravenously with an increase in blood pressure, a lowering of heart rate and improved mental state and diuresis, the amount of given fluid was enough for this moment. Blood lactate levels may also be helpful to assess clinical deterioration or improvement of a patient over time, but one should realise that lactate can be increased as a result of anaerobic glycolysis due to systemic or regional hypoperfusion, but also due to stress-related adrenergic-induced aerobic glycolysis, impaired hepatic clearance as well as mitochondrial dysfunction limiting pyruvate metabolism. One should therefore never focus on a single parameter such as lactate alone to assess the effect of treatment and there is insufficient convincing evidence that decreasing lactate levels alone is a useful target of therapy in critically ill patients (Bakker 2014).

> **RCTs on vasoactive drugs, aiming at specific figures, or even comparing different figures of blood pressure, lack sufficient acknowledgement of physiological facts**

Goal for blood pressure: enough

For the treatment of shock, blood pressure has been and is a pivotal marker of severity of shock and effectivity of treatment. As outlined before, we argue that blood pressure should be just enough. Now it is clear that "enough" is different and a higher value in a patient with shock and a history of insufficiently treated hypertension compared to a person who is used to a blood pressure of 105/70 mmHg and has a blank medical history. Furthermore, since all treatments involved such as fluid resuscitation and the administration of vasoactive drugs are known to produce important side-effects such as oedema and arrhythmias, which are also dose-dependent, it becomes clear that the lowest possible dose/quantity should be given: the definition of "enough". Only in this way will the advantages outweigh the disadvantages for the patient. We have therefore reasons to believe that RCTs on vasoactive drugs, aiming at specific figures, or even comparing different figures of blood pressure, lack sufficient acknowledgement of physiological facts. The recommendations of the Surviving Sepsis Campaign to maintain a mean arterial pressure (MAP) of 65 mmHg in septic shock may be of use for paramedics and inexperienced physicians, but as follows from the previous text should not be used by experienced intensivists who are aware of the cardiovascular physiology and heart-lung interactions.

However, things are not that simple. The blood pressure that is enough for the brain might not be enough for the kidneys or vice versa. Some organs such as the brain, heart and kidney are known to have some ability to auto-regulate blood flow resulting in a constant blood flow across a specific MAP range (Hollenberg 2011). But this can be deranged in different situations, such as brain injury, pre-existing hypertension or abdominal compartment syndrome. Therefore it is of utmost importance to evaluate clinical signs and markers of tissue perfusion continuously. Measurement of cardiac output can be complementary to understand the present (circulatory) physiology of the patient, either done by thermodilution with a pulmonary artery catheter, or combined with continuous pulse contour analysis through an arterial cannula, or noninvasive using cardiac ultrasound or pulse contour analysis. Cardiac output should not be aimed at a specific target, but again should be "enough" and certainly not too high, as has been previously advised for supra-normal goals of therapy.

Use of vasoactive drugs

In clinical practice, to determine which vasoactive drug to administer, the desired effect has to be determined as well as knowledge about the required receptors or other cellular pathways involved. Unfortunately, there is not such a drug that 100% specifically stimulates only one type of receptor. And most adrenergic drugs have a combined effect on both α- and β-adrenergic receptors. To increase arterial blood pressure an adrenergic drug that has a predominant α1-adrenergic effect is required, or a drug that stimulates another receptor or pathway such as angiotensin II or vasopressin. In cardiogenic shock, low cardiac output state or other types of impaired cardiac function (where cardiac output is "not enough"), an agent may be required that has affinity for

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β1-adrenergic receptors to increase inotropy, chronotropy or dromotropy. There are also other cellular pathways to increase the cardiac contractility via other routes, such as increasing intracellular calcium or affinity of cardiac myocytes for calcium. It is good to realise that any drug has potential adverse effects. Vasopressor therapy can result in decreased stroke volume and thus cardiac output because of the increased afterload.

During inotrope use arrhythmias might occur, and cardiac oxygen demand might be increased because of increased heart rate. Inotropes can also cause vasodilatation requiring additional vasopressors to maintain adequate blood pressure. In general, short-acting vasoactive drugs should be titrated to effect to achieve specific haemodynamic goals while minimising potential harmful effects.

We provide a brief overview of the pharmacotherapy with vasoactive drugs in critical care medicine in an attempt to summarise cellular effects, indications, common adverse effects as well as recent scientific evidence, for both proven drugs and newer agents.

Adrenaline (Epinephrine)

Adrenaline is an endogenous hormone and neurotransmitter produced by and stored in the adrenal glands. It has a main effect on the β_1 receptor, with additional affinity for β_2- and α_1- adrenergic receptors, resulting in both increased cardiac output and mean arterial pressure. The main difference beween adrenaline and noradrenaline (norepinephrine) is the increased affinity of adrenaline for β_2-receptors compared to noradrenaline. Low doses of adrenaline result in an increase of cardiac output and variable effects on mean arterial pressure, depending on the balance of effects of β_1, β_2 and α_1 adrenergic receptors stimulation.

It is short acting and mostly metabolised in the liver by catechol-O-methyltransferase (COMT) and monoamine oxidases (MAO). Excretion of metabolites is renal. Because of strong β_1 effect, arrhythmias are common during use. Lactic acidosis is often reported, which is a direct β_2 adrenergic effect.

Current indications for the use of adrenaline in critically ill patients are during cardiac arrest, anaphylactic shock and as an adjunctive antihypotensive agent. There are few trials that compare adrenaline to other agents, of which two larger studies can be mentioned. One randomised controlled trial (RCT) (n=280) compared adrenaline to noradrenaline in septic shock and found no difference in survival but a higher incidence of tachyarrhythmia and lactic acidosis in the adrenaline group (Myburgh et al. 2008). Another RCT (n=330) compared adrenaline and a noradrenaline/dobutamine combination and concluded there was no difference in safety and efficacy (Annane et al. 2007).

In cardiopulmonary resuscitation adrenaline appears to increase the chances for return of spontaneous circulation, but does not increase favourable neurological outcome. A very recent placebo-controlled RCT confirmed these findings, with adrenaline improving 30-day survival, but no difference in proportion of patients surviving hospital discharge with a favourable neurological outcome (Perkins et al. 2018).

Noradrenaline

Noradrenaline is also an endogenous hormone and neurotransmitter. Its main affinity is for α_1-adrenergic receptors, with some β_1 and minor β_2 effects. Noradrenaline has a short half-life; it is active for about 1-2 minutes. Metabolism is hepatic and in nerve endings and inactive metabolites are excreted renally. Noradrenaline is used mainly as a vasopressor in vasodilatory shock, but also cardiogenic shock and during general anaesthesia for anaesthesia-induced hypotension. Adverse effects are mainly related to severe vasoconstriction, such as limb or gastrointestinal ischaemia. A widespread misunderstanding is that noradrenaline decreases coronary blood flow (Mueller et al. 1970). The comparison of noradrenaline versus dopamine in the treatment of septic shock seemed more favourable towards noradrenaline looking at clinical trials (De Backer et al. 2012)

Dopamine

Dopamine is the endogenous precursor of (nor) adrenaline and has a complicated action on the cardiovascular, renal and neurohumoural systems. Metabolism is fast, elimination half-life is 1-2 minutes with metabolism in the liver, kidneys and plasma by MAO and COMT into inactive metabolites and noradrenaline. Metabolites are excreted by the kidneys. The circulatory effect depends on the predominant effect of the different receptors that are stimulated by dopamine: dopaminergic receptors (DA1, DA2), β_1- and α_1-adrenergic receptors (Girbes et al. 2000). Some authors wrongly still write that dopamine stimulates different receptors at different doses, distinguishing 1-4 µg/kg/min, 4-10 and >10 µg/kg/min. This is simply not true. At every dose dopamine stimulates DA1, DA2, β_1- (β_2), and α_1-adrenergic receptors. Additionally, dopamine inhibits uptake-1. In the past the positive effects of dopamine were overrated, mainly related to its effects on renal blood flow (Girbes and Smit, 1997). Dopamine was given at "a renal dose", i.e. a dose up to 4 µg/kg/min to preserve renal function, but later studies indicated no beneficial effects in the long-term (Marik 2002). And since the RCTs comparing noradrenaline and dopamine, the use of dopamine is significantly reduced, due to its reported side-effects, mainly dysrhythmias.

Dobutamine

Dobutamine is a mixture of two isomers with mainly β_1, but also β_2 and mild α_1-adrenergic receptor effects. Elimination half-life is 2 minutes, metabolism is mostly by COMT in the liver and tissues into inactive metabolites that are excreted by the kidney. The main effect of dobutamine is as an inotrope through β_1-receptor effects: an increase in cardiac output by increasing stroke volume and heart rate. Effects on blood pressure vary and are unpredictable (Hollenberg 2011). Because of the positive chronotropic and inotropic effect on the heart, dobutamine causes an increase in myocardial oxygen demand, with a risk of myocardial ischaemia. Ventricular arrhythmia may also occur.

Dobutamine is an agent widely used in cardiogenic shock, and gained popularity as an agent used in septic shock since the original early goal-directed therapy (EGDT) trial where it was used to achieve central venous oxygen saturation goals (Rivers et al. 2001). It was only realised later by intensivists that the Rivers study population was not a representative population of patients with sepsis. Many other large studies proved no benefit for the use of dobutamine as deemed indicated according to the EGDT guidelines (Mouncey et al. 2015).

Vasopressin and analogues

Antidiuretic hormone, also named arginine vasopressin (AVP), is an endogenous hormone secreted by the anterior pituitary gland in response to stress or shock. There are three major vasopressin receptors and for conditions of circulatory shock the vasoconstrictor effect of smooth muscle caused by activation of the V_1 receptor is most relevant. AVP is given intravenously and has a half-life of 10-35 minutes with V_1, V_2 and V_3-receptor affinity. It is rapidly metabolised by the liver and kidney.

Terlipressin is a non-selective vasopressin analogue that also is a prodrug of lysine vasopressin, which is similar to AVP. The elimination half-life is 50 minutes, with active metabolites for up to 6 hours. Vasoconstriction caused by V_1 receptor stimulation could lead to additional cardiac ischaemia and is possibly more pronounced in the mesenterial region resulting in gastrointestinal ischaemia. Reflex bradycardia may lead to decreased cardiac output. V_2-receptor activation causes endothelial von Willebrand factor release, causing enhanced platelet aggregation with increased risk for thrombosis. (Saad and Maybauer 2017).

Selepressin is a novel, short-acting selective V_1 agonist that appears promising in initial studies, but a critical appraisal of new data must be awaited. In animal sepsis models, improved survival compared to noradrenaline is reported. And importantly, a decrease in pulmonary capillary leak (Saad 2017).

There is no convincing evidence that vasopressin or its analogues are superior to catecholamines in the treatment of sepsis or during cardiopulmonary resuscitation. Vasopressin can however be considered as a second-line vasopressor therapy. The vasopressin analogue terlipressin is commonly used in hepatorenal syndrome and portal hypertension but there is no convincing evidence supporting its use in septic shock. The clinical relevance of studies showing that vasopressin reduces the use of noradrenaline are in our view questionable.

Angiotensin 2

Synthetic (or bovine) angiotensin II is a novel drug that is postulated as a third type of vasopressor, after adrenergic vasopressors and vasopressin. Angiotensin II is converted from angiotensin I by angiotensin-converting enzyme (ACE) and a product of the renin-angiotensin-aldosterone system (RAAS), which is activated by decreased renal perfusion in hypovolaemia. Angiotensin II has a vasoconstrictor effect by increasing intracellular calcium levels in smooth muscle cells that results in vascular contraction after activating several cell-signaling pathways. There is however, little evidence supporting the use of angiotensin II in shocked critically ill patients. The recent *Angiotensin II for the Treatment of High-Output Shock* (ATHOS-3) trial investigating the addition of angiotensin II to noradrenaline in the treatment of "refractory" vasodilatory shock in 344 patients showed a significant increase in blood pressure and decrease of noradrenaline dose in the study group. However, there is a lack of data on serum lactate or central venous oxygen saturation and, most importantly, none of the patients was in fact treated with high-doses vasopressor therapy at the beginning of the study. There were no significant differences in mortality or adverse events (Khanna et al. 2017).

> "it is of utmost importance to evaluate clinical signs and markers of tissue perfusion continuously"

Nitric Oxide (NO) inhibitors

Systemic inflammation can cause the overexpression of "inducible nitric oxide synthetase" (iNOS), which is stimulated by pro-inflammatory cytokines, resulting in excess nitric oxide and vasodilatation. Attempts have been made to counteract this overexpression. However, clinical trials have been disappointing and at this moment there is no place for the use of NO-inhibitors in the treatment of septic critically ill patients.

Phosphodiesterase inhibitors: milrinone and enoximone

Frequently used phosphodiesterase inhibitors (PDEi) in the ICU are enoximone and milrinone. Both inhibit phosphodiesterase type III, resulting in an increased amount of intracellular cAMP, which leads to an activation of cardiac calcium channels and increased calcium influx during systole increasing cardiac contraction force. During diastole, there is an increased efflux of calcium increasing relaxation (lusitropy). Because of the inotropic and vasodilatory effects, PDEi are also called inodilators. Excretion is mostly renal, and half-life depends greatly on kidney function, with the risk of accumulation. Known adverse events include tachyarrhythmia, thrombocytopaenia and hypotension. Although many studies found an improvement of circulatory parameters in patients with (severe) heart failure in the short term, later studies showed that this was not translated into a better long-term outcome. For patients after cardiac surgery that require inotropic support, there is also a possible trend towards greater mortality compared to dobutamine (Nielsen et al. 2018).

Levosimendan

Levosimendan is a calcium sensitiser: it increases the susceptibility of cardiac myocytes to calcium by binding on troponin C, resulting in increased cardiac contraction without increasing calcium levels. There is no change in diastolic relaxation or increase in myocardial oxygen demand. Another effect is vasodilatation by opening vascular smooth muscle cells as a result of opening ATP-sensitive potassium channels. The biological half-life is about 1 hour and active metabolites after conjugation with glutathione, the metabolites are pharmacologically inactive and excreted in urine and faeces. Some metabolites, 4-7% of the levosimendan dose, are formed slowly and the elimation half-life has been up to 70-80 hours in patients with congestive heart failure. A single day of infusion is adequate for several days of treatment. It is therefore not surprising that the use of levosimendan has been associated with higher incidence of tachyarrhythmia and prolonged hypotension (Antila et al. 2007). Initial enthusiasm about the application of levosimendan for either low cardiac output states or sepsis has been denied by later and larger studies.

Other agents

Phenylephrine is mainly an α_1-agonist, that is used mainly in theatre for perioperative hypotension. Because of the increase in systemic vascular resistance (SVR) and subsequent

baroreceptor-induced decrease in heart rate, its net effect is a decrease in cardiac output. Ephedrine is an indirect agent that stimulates the release of endogenous noradrenaline. Repeated doses show decreased effect known as tachyphylaxis, caused by a depletion of cellular noradrenaline stores. Data on patients in the ICU are scarce and there are no data to justify prolonged administration in the ICU. Isoprenaline is a short-acting nonselective beta agonist that is mostly used in treatment of extreme bradycardia and atrioventricular block.

Special considerations

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) has obtained more attention in the ICU with a focus on right ventricular (RV) function. In critically ill patients with pulmonary hypertension and (imminent) RV failure, the goal of treatment is to reduce pulmonary vascular resistance, improve right ventricular contractility, optimising right ventricular preload while also maintaining adequate systemic perfusion. Fluid management requires special attention since in the case of increased RV afterload, volume loading will result in RV dilatation and displacement of the interventricular septum toward the left ventricle (LV) with impaired LV diastolic filling as well as decreased right coronary perfusion. Failure to take this into account will thus result in deterioration of the circulation with deleterious consequences. The most important factor is to establish the diagnosis as soon as possible in order to be able to provide adjusted precision therapy. Cautious fluid resuscitation (including no extra fluid administration) is an important factor for that and the reader is referred to a recent review (Jentzer and Mathier 2016). The goals for vasoactive medication include reduction of PVR, maintenance of SVR and increased cardiac output. PDEi inhibitors have favourable effects compared to dopamine and dobutamine as a result of increased right ventricle contractility and pulmonary vasodilatation with less tachycardia and additional oxygen consumption. The decrease of SVR and concomitant decrease of systemic blood pressure may be treated with a vasopressor such as noradrenaline. However, all α-1 agonists are reported to increase PVR, with a possible increase in right ventricular afterload. Vasopressin has a moderate additional and considered favourable effect of endothelin-dependent pulmonary vasodilation, thereby producing less increase of PVR compared to the increase of SVR. Intravenous prostanoids are indicated for patients with critical PAH, with a preference for prostanoids with a short half-life e.g. epoprostenol.

Hepatic failure

Patients with hepatic failure are often volume depleted as a result of low systemic vascular resistance (vasodilation), together with a high cardiac output, and it mimics vasodilatory shock. Few studies have been conducted comparing different vasoactive drugs in the critically ill with hepatic failure, and most have very few patients. After volume resuscitation, noradrenaline is usually recommended because of its less outspoken constrictor effect on the splanchnic circulation. Vasopressin or terlipressin can be added to potentiate noradrenaline. There is insufficient reason to believe that terlipressin is superior to other vasoactive drugs in case of hepatorenal syndrome (Israelsen et al. 2017).

Traumatic brain injury

In physiological conditions, the brain has the ability to auto-regulate cerebral blood flow. After TBI, cerebral autoregulation could be impaired, and therefore a pivotal treatment goal in the critical care setting is to maintain adequate cerebral perfusion. A commonly used parameter to guide treatment is cerebral perfusion pressure, which is the function of mean arterial pressure minus intracranial pressure measured by an intraventricular or intraparenchymal probe. The recommended cerebral perfusion pressure is between 60-70 mmHg (Carney et al. 2016). There are no high-quality studies indicating which vasoactive drug is best used to increase arterial pressure in TBI patients. Noradrenaline has the most predictable effects.

Discussion

Treatment of critically ill patients is micromanagement of all vital functions. The use of vasoactive medication is only a part of the treatment of a complex pathophysiology. Because of the immense heterogeneity amongst patients, the increasing choice between different agents and the supportive nature of treatment with vasoactive drugs, comparing treatments is challenging and prone to error. Although we acknowledge the huge efforts and organisational skills to perform RCTs with vasoactive drugs, we question the value in terms of external validation and applicability, especially in view of individual precision medicine, for the reasons mentioned above. The value of such trials is therefore in our opinion merely on the collection of data of side-effects. Furthermore, one should realise that if such trials compare different strategies of the use of vasoactive drugs, the outcome applies only for that specific strategy with those defined haemodynamic goals. In other words, if a trial says that noradrenaline is "better" than dopamine, it is only applicable if you use the specific haemodynamic goals in a similar population. And the result might be different if you use a slightly different haemodynamic goal for dopamine or noradrenaline. We also foresee that the answer on which is the best vasoactive medication for my patient, or groups of patients, will never come from large RCTs. Recommendations with fixed figures such as in the Surviving Sepsis Campaign are perhaps of use for non-intensivists, but are potentially dangerous and ignore the complexity of disease in individual critically ill patients. Therefore, understanding the pathophysiology, watching carefully and continuously the effect of the given therapy, doing all (simple) things right will for the coming decades remain the cornerstone of therapy with vasoactive medication, but it will be called precision medicine. ■

Conflict of interest

Jon Gutteling declares that he has no conflict of interest. Armand R.J. Girbes declares that he has no conflict of interest.

Abbreviations

MAP mean arterial pressure
PVR pulmonary vascular resistance
SvO_2 mixed venous blood oxygen saturation
SVR systemic vascular resistance
VR venous return

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Advances in source control in patients with sepsis and septic shock

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In the past decades there have been significant advances in the diagnosis and management of patients with sepsis and septic shock, and overall awareness has increased significantly (Angus and van der Poll 2013). Emphasis is currently on the early detection of sepsis and rapid initiation of fluid administration and antibiotic therapy, all of which have improved outcomes (Rhodes et al. 2017). Nevertheless, discussion remains about the targets for fluid resuscitation, the optimal type of fluid and many other aspects of sepsis management, and this directs scientific research in the field (Perner et al. 2017).

While there is consensus that antibiotic therapy and source control are the major therapies for severe infections, source control has been consistently ignored by many studies, and its exact role, particularly the timing and methodology used, remains uncertain. Source control is receiving only limited attention in the first hour of sepsis treatment, disproportional to its impact on outcome. It has proved hard to accurately define source control, and quantifying it is even more difficult. But insights into the role of source control are evolving, and both the epidemiology and methodology will surely receive more consideration in the next years. Currently, exact data on the impact of source control, or data that provide adequate guidance on the timing and preferred method for source control remain scarce.

1. Defining source control

The definition of source control has not changed over the years, yet this definition is more a conceptual approach, focusing on the goal of source control rather than the exact method to reach these goals. Source control is defined as the different measures that are used to eliminate the source of an infection, control ongoing contamination and restore premorbid anatomy and function (Schein and Marshall 2002). It is true that source control is most often thought of in patients with abdominal infections because of the ongoing contamination (De Waele 2016) but source control should be considered in every patient with sepsis or septic shock. In fact, up to 45% of patients with sepsis and septic shock require some form of source control (Bloos et al. 2017). Not every patient of course may require a surgical procedure, but also in patients with presumed non-surgical infections source control may be considered e.g. in patients with bloodstream, urinary tract or respiratory infections.

> **"source control has been consistently ignored by many studies and its exact role remains uncertain"**

Most of the time the focus is on the first two goals of source control, namely eliminating the source of infection and controlling ongoing contamination. Source control can involve a surgical procedure, percutaneous drainage using a catheter (that either remains in place or not), incision of an abscess, removal of necrotic tissue or removal of an infected device e.g. central venous catheter or external ventricular drain.

Historically, the evidence came from non-randomised controlled trials, mainly in necrotising fasciitis, with multiple case series conducted in the 1990s (Elliott et al. 1996). The data were in favour of an aggressive operative approach. An expert opinion roundtable in the mid 2000s highlighted that appropriate source control should be part of the systematic checklist we have to keep in mind in setting up the therapeutic strategy in sepsis (Marshall et al. 2004).

A practical approach to define source control is rather ambiguous in some guidelines. For instance, in the recent Surviving Sepsis Campaign (SSC) guidelines from 2016 the recommendation was:

> *We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made* (Rhodes et al. 2017).

Interestingly the recommendation was acknowledged as a "Best Practice Statement".

2. Source control in critically ill patients

Applying source control and its principles

Table 1. Different source control measures and matching clinical scenarios

Source control measure	Clinical scenario
Excision	Appendicitis, cholecystitis
Repair	Perforated ulcer, early iatrogenic injury
Diversion +/- excision	Leaking anastomosis
Drainage	Abscesses or infected fluid collections
Debridement	Necrotic infected tissue

Table 2. Different interventions and their effectiveness on source control principles

Intervention	Drainage	Debridement	Restoration of anatomy and function
Open surgery	+++	+++	+++
Percutaneous drainage	++	+	0
Device removal	+	0	0
Desobstruction	++	0	++
Open abdomen management	++	0	0

in critically ill patients poses specific challenges. First, the patient is more severely ill, with less room for compensating for the consequences or complications of a procedure; second, the urgency of the need for source control is equally different. Leaving a patient exposed to an untreated infection can have more severe consequences compared to patients who present without sepsis, even if antibiotic therapy and fluid resuscitation have been initiated.

The proportion of patients with sepsis that requires source control clearly depends on the type of infection that is causing sepsis. In the multicentre study by Bloos et al. (2014), 42% of patients with septic shock required source control. In this study, the majority of these procedures was surgical (85%), but this may vary according to the source of the infection, presence of ongoing contamination, surgical history and general condition as well as co-morbidities of the patient.

3. Available methods for source control

Based on the aspect that source control consists of those definitive measures to control a source of ongoing microbial contamination and to restore anatomy and function, definition of source control can be integrated in five categories (**Table 1**).

Source control has long been synonymous with a surgical procedure, mostly a laparotomy or other open intervention, but this is changing significantly. Firstly, laparoscopy and minimally invasive procedures have replaced open surgical procedures, although in critically ill patients laparoscopy may be less tolerated. The main evolution regarding source control has been the rise of percutaneous drainage of abscesses in many locations, either ultrasound or CT-guided (Soop et al. 2017). **Table 2** provides an overview of the different interventions and how effective they are in regard to the different source control principles.

- **Open or endoscopic surgery** is still the most controlled method of source control. It is very effective in completely draining collections or abscesses and debriding necrotic tissue. Also, restoration of anatomy and function is straightforward.
- **Percutaneous drainage (PCD)** is effective in draining a large part of most collections, although mostly a small residual amount will remain. This is often managed by rinsing the catheter and collection in order to remove the last remainders of the infection. For multiloculated infections multiple catheters may be needed, and also more residual infection may have to be tolerated. Implicitly the residual infection may continue to produce signs and symptoms of infection and the response to the treatment may be more difficult to monitor. Debriding necrotic tissue is even more difficult and again a considerable amount of necrosis may need to be tolerated. Repairing anatomical lesions is not possible using PCD.
- But also simple interventions such as **device removal** can be considered for source control. Removing an obstruction such as a urinary tract lithiasis or choledocholithiasis can be effective in draining the infection, but again no meaningful debridement is possible. Anatomy and function are mostly adequately restored after such a procedure. Open abdomen management can also be part of a source control procedure, effective mostly for draining the abdominal cavity. Restoration of anatomy and function will only follow later.

Strategies for source control are improving continuously and no doubt will do so in the future. The trend towards minimally invasive procedures will continue, with more advanced endoscopic (ultrasound-guided) procedures as the most important development. As an example, transgastric endoscopic drainage and necrosectomy for infected pancreatitis (van Brunschot et al. 2018) is a promising technique that obviates the need for open surgery, often fraught with complications.

It remains to be demonstrated that patient condition makes no difference in selecting the best source control procedure, and in studies reporting on new techniques severity of illness should definitely be considered to make sure that the most vulnerable patient benefits from the most optimal procedure.

4. Importance of source control

Data supporting the role of source control are limited although several studies have recently focused on this important issue. From these data, two relevant aspects are consistently reported: source control adequacy and timing of the intervention.

The impact of source control seems to be unrelated to the administration of appropriate antibiotics. Several studies found that both are

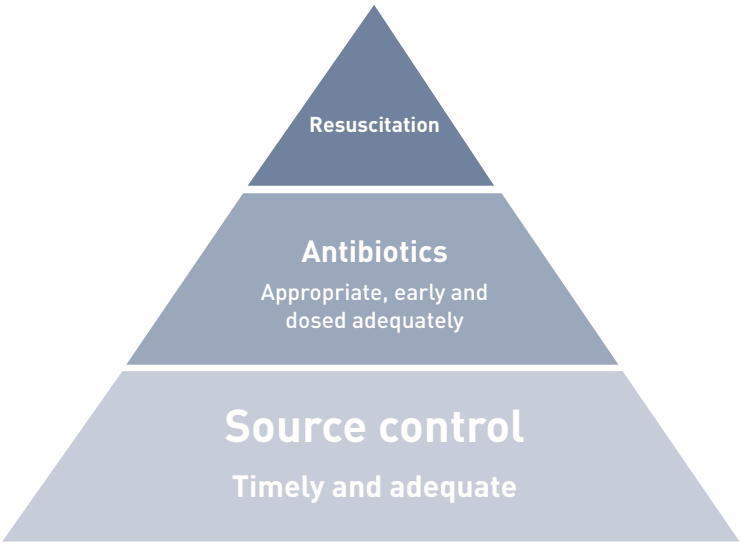

Figure 1. Relation of different interventions for sepsis and septic shock

independent predictors of mortality (Bloos et al. 2015; Tellor et al. 2015), but there is consensus that without adequate source control, antibiotic therapy may have little if any effect (**Figure 1**).

a) Adequacy of source control

Inadequate source control seems to be a relatively frequent problem, but source control has been inconsistently defined in the literature, and often there is even no definition or description provided. Source control adequacy is determined by source of infection, source control intervention, patient type, definition used, methodology applied among other factors.

Logically, not controlling the source of infection should be included in a definition of inadequate source control, but there is no consistency in other elements of source control adequacy. Some definitions include both timing (e.g. within 24h) as well as pure technical considerations (did the surgical procedure result in control of the ongoing infectious process?) (Tellor et al. 2015), whereas others fail to have a clear definition of source control (Bloos et al. 2014; Coccolini et al. 2015; Martínez et al. 2017).

Data on the extent of the problem in critically ill patients is unclear. In patients with complicated diverticulitis, source control adequacy was reported to be as high as 91% (Coccolini et al. 2017). Bloos et al. (2014) reported 86.7% source control adequacy although no clear definition was provided ("unsuccessful procedure"). In some studies source control adequacy is evaluated by a panel of surgeons (Tellor et al. 2015), whereas in other studies this is not specified (Coccolini et al. 2015; Bloos et al. 2014).

Given the importance of source control, a clear definition of source control adequacy and methodology used is essential in order to better understand the role and develop the best approach to patients requiring source control interventions.

A final comment would be related to the integration of the new concepts in surgery such as damage control, as on many occasions source control is not feasible from the start (Leppäniemi et al. 2015). This concept has been advocated based on experience of damage control laparotomy patients with severe abdominal trauma and it is a limited procedure to control the infection with four practical strategies (**Table 3**). This approach has also been named rapid source control laparotomy (Becher et al. 2016).

The antibiotic strategy differs depending on the success in achieving source control. Whilst in patients with adequate source control, antibiotics can be used as an adjunct to source control, to prevent dissemination of pathogenic microorganisms during source control procedures and to eradicate residual pathogens after those procedures, in patients with incomplete source control, antibiotics remain as the primary modality for the treatment of the infection.

b) Timing of source control

Delayed source control can be caused by a delay in diagnosis or in intervention after a correct diagnosis has been made; evidently both require different interventions. An accurate and rapid diagnostic process in patients with sepsis or septic shock, which runs in parallel with the resuscitation and other interventions is key for the former; for the latter, often organisational issues such as operating room or interventional radiology availability may be the primary reason.

The rationale for rapid source control is straightforward (**Figure 2**), yet few guidelines provide clear and evidence-based guidance on the timing of source control in patients with sepsis or septic shock. The SSC guidelines recommend controlling the source of the infection as soon as medically and logistically practical after the diagnosis is made (with the suggestion to do so within a 6-12-hour window after diagnosis) (Rhodes et al. 2017), whereas the English Royal College of Surgeons recommends controlling the source of the infection within 6 hours in patients with sepsis and immediately in patients with septic shock (Royal College of Surgeons of England 2011). The latest update of the Surgical Infection Society guideline on intra-abdominal infections cites 24 hours as the window in which the source needs to be

Table 3. Elements of damage control surgery in abdominal sepsis

Resection without re-anastomosis or ostomy formation
Temporary drainage
Abdominal packing if needed
Temporary abdominal closure

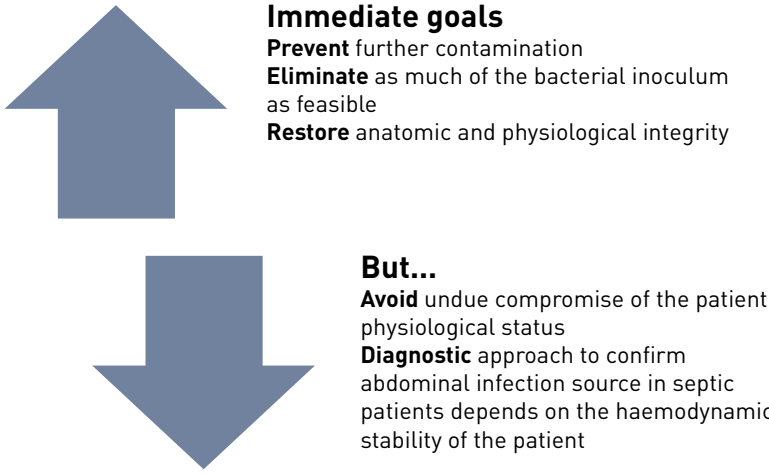

Figure 2. Rationale for rapid source control

controlled, unless when patients have sepsis or septic shock, when the intervention needs to be undertaken in a more urgent manner (Mazuski et al. 2017).

Timing is a critical aspect of source control. A UK study found that in general surgery patients, the median time to surgical source control was 19.8 hours, with no difference in patients with sepsis and septic shock compared to patient without sepsis (as per current definitions) (UK National Surgical Research Collaborative 2017). In a study on patients with complicated diverticulitis of different degrees of severity, one third of source control procedures was delayed for more than 24h (Coccolini et al. 2015). In another large-scale observational study including more than 4500 patients, delay of source control beyond 24h was present in almost half of the survivors, and more than 80% of non-survivors (Sartelli et al. 2015).

In a Korean study on emergency department (ED) patients with septic shock, the majority of patients received source control within 12 hours after ED arrival; in this study the timing of source control did not impact outcome (Shin et al. 2017). A Spanish multicentre study also could not link source control timing (interval between sepsis or septic shock diagnosis to intervention) to worse outcome (Martínez et al. 2017). Again, the majority of the patients' time to source control was short: median time to source control was 4.6 hours, with 76% of patients receiving source control within 12 hours.

Bloos et al. (2014) found that the median time from onset of severe sepsis or septic shock to source control in a large sample of German ICU patients was 2 hours in survivors and 5.7 hours in non-survivors. Time to source control of more than 6 hours was independently associated with increased mortality (as were age and disease severity) in patients who required source control (Bloos et al. 2014). Time to interventional source control was twice that of surgical source control (6 hours vs. 3 hours).

Bloos et al. (2017) found that source control was significantly related to 28-day mortality and reported a 1% increase in mortality per hour delay of surgical source control. In patients with abdominal sepsis and associated bacteraemia, inadequate and delayed source control was more frequent in non-survivors; inadequate source control and inappropriate antibiotics were independently associated with mortality, but the adjusted odds ratio for inadequate source control was twice as high as for inappropriate antibiotics (Tellor et al. 2015).

Coccolini et al. found delayed source control (>24h) as the sole factor associated with worse outcome in patients with complicated diverticulitis (Coccolini et al. 2017).

Based on the available evidence it could be concluded that the biggest gain in improving outcome is in patients in whom source control is delayed beyond 12-24 hours. It would be very challenging to reduce the timing to source control further in many situations, as also the delay in source control may be explained by other patient factors rather than institutional factors alone.

6. Where are we going from here?

It is clear that source control is an important determinant of outcome, but its exact role in critically ill patients, and the relevance of aspects such as timing and methodology of source control requires more attention. This will help us to provide evidence-based recommendations and may also inform targeted randomised studies on this topic. In the context of severely ill patients, not only the factors related to the intervention but also the patient condition, site of infection and relevant co-morbidities may be highly significant in determining outcomes.

Based on the complexity of severe illness, the range of infections where source control is relevant and the choice of source control interventions at our disposal, it is clear that a generalised approach will be inadequate and a highly personalised, carefully timed approach is the best path to follow. ■

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Organ cross-talk in shock and critical illness

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Organ cross-talk is a popular mechanism invoked to explain the progression of multi-organ dysfunction syndrome; however this term is often ill-defined and may encompass many differing mechanisms of organ interaction. In this article the concept of cross-talk is reviewed and its real meaning to the clinical is critically appraised.

Multi-organ failure, better termed multi-organ dysfunction syndrome (MODS)— reflecting a graduation in severity of organ injuries, is one of the defining features of critical illness. MODS is a frequent consequence of presentation with circulatory or septic shock, or as a serious complication of organ hypoperfusion and systemic inflammatory responses during major surgery. Even when the reason for ICU admission is only to support a single organ system there is invariably potential for dysfunction of other organ systems, either directly, due to the primary disease, or indirectly from the distant effects of the primary organ failure or of organ support therapies such as sedation or invasive mechanical ventilation. Managing the conflicting demands of multi-organ support is the bread and butter of modern critical care and intensivists are very familiar with the concept of escalating increase in risk of death with the presence or acquisition of additional 'organ failures' (Ferreira et al. 2001). There has been a longstanding appreciation of the importance of providing effective early treatment of primary conditions while avoiding secondary injury to prevent a spiral toward progressive organ dysfunction and death. More recently, there has been an interest in the bi-directional impact of organ dysfunction and its treatment on the function of other organ systems, a process termed "organ cross-talk." Behind this concept lie two important observations: firstly that organ injuries may potentiate, resulting in a far greater burden of illness than if the effects of dysfunction of different organs were merely added, and, secondly, that there may be specific pathophysiological pathways of organ cross-talk that could be targets for specific intervention. However, while "organ cross-talk" is becoming a widely used term, it is often employed with little detailed understanding. It could mean many things in differing circumstances. Clearly, 'cross-talk' between organs is part of the normal physiology of a large multicellular organism, with physiological mechanisms responsible for maintenance of whole organism homeostasis. Examples of such mechanisms include neurological and endocrine signalling between organs and the direct effects of physiological parameters such as blood pressure or arterial oxygen content on the function of distant organs.

> "while "organ cross-talk" is becoming a widely used term, it is often employed with little detailed understanding"

It is the breakdown of such homeostatic mechanisms that is another defining feature of critical illness. Furthermore, coordinated responses to inflammation across many organ systems are part of the physiological responses to injury, but represent a form of communication between biological systems. While it is pathological forms of cross-talk, where responses in one organ are deleterious to the function of another that have been the focus of most interest, we should not forget that loss of normal physiological cross-talk between organs may play an equally important role in the progression of multiple organ dysfunction.

For the bedside clinician what then distinguishes pathological organ cross-talk from MODS in general? Pathological organ cross-talk is one mechanism by which MODS can arise or progress. MODS can arise in parallel with a systemic insult such as septic or haemorrhagic shock affecting many organs simultaneously. In this case such mechanisms affect supply/demand imbalance of organ perfusion and the inflammatory response to circulation damage or pathogen-associated molecular patterns are 'talking' to multiple organs simultaneously (**Figure 1a**). Conversely in cases where organ dysfunction arises in series as the effect of severe injury to one organ goes on to cause dysfunction in a number of other organ systems in a form of predominantly unidirectional cross-talk, an example is the systemic effects of cardiogenic shock (**Figure 1b**). However, irrespective of whether MODS arises in series or parallel, bidirectional effects of organ injuries and dysfunction on other organ systems is a key aspect of the progression of MODS, eventually culminating in refractory shock and death (**Figure 2**). In addition to acute organ dysfunction chronic organ disease may play an important modifying role in the development of MODS, in critical illness (**Figure 3**), firstly by increasing risk of developing organ failure in response to distant injury, both in decompensation of

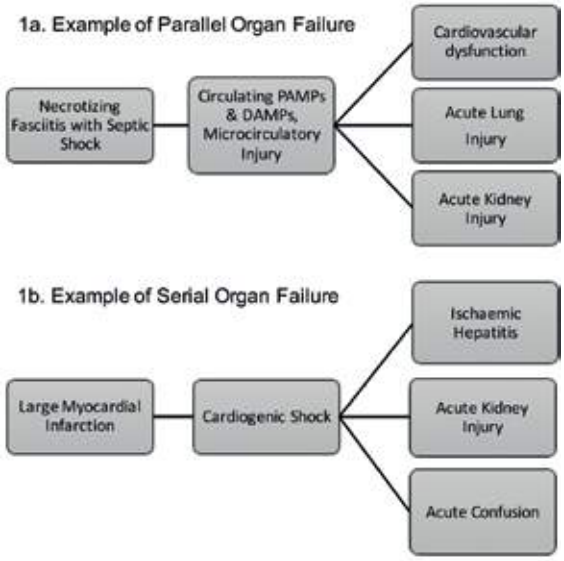

Figure 1. Examples of models of multi-organ dysfunction syndrome (MODS) in shock

MODS may arise primarily in parallel from a major systemic insult (1a) or in series from the effects of a major primary organ dysfunction (1b) and be mediated primarily by circulating mediators (1a) or by distant physiological effects of organ injury (1b).
DAMPs damage pathogen associated molecular patterns PAMPs pathogen associated molecular patterns

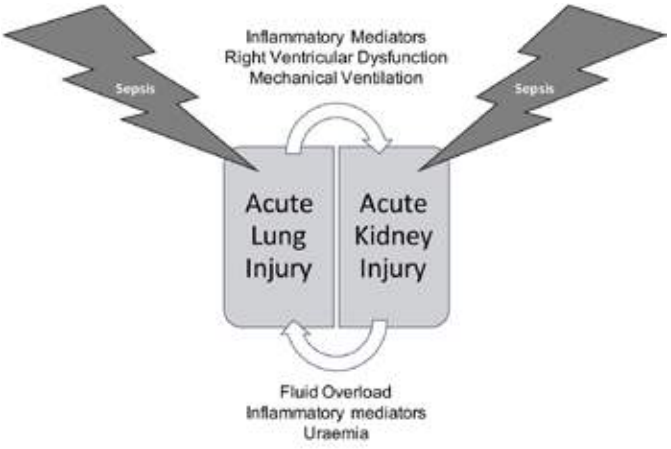

Figure 2. Organ cross-talk potentiates the severity of organ dysfunction after systemic multi-organ insult

Both circulating mediators (damage and pathogen associated molecular patterns, cytokines and other mediators) and physiological effects as well as effects of organ support may mediate this process

the chronically diseased organ (i.e. decompensation of chronic liver disease in sepsis) and in acquisition of acute injury in other organs (i.e. predisposition to acute kidney injury in the context of chronic liver or cardiac disease). Finally, we cannot neglect the effects of treatment for organ dysfunction on other organ systems: interventions such as mechanical ventilation, sedation, renal replacement therapy and extracorporeal membrane oxygenation may be necessary for the treatment of one organ system, but have unintended deleterious effects elsewhere, while the presence of other organ dysfunctions can complicate the application and use of such methods of organ support, a process of so-called artificial organ cross-talk (Husain-Syed et al. 2018). Of course, in most cases of critical illness many or all of the above mechanisms co-exist, so that MODS typically arises in part in series and in part in parallel on a background of some chronic co-morbid disease, potentiated by bidirectional effects of organ injuries and modified by the positive and negative effects of organ support therapies.

Given the diversity of pathological organ cross-talk it's not surprising that multiple mechanisms have been invoked to explain it. Broadly these could be considered as the distant effects of inflammatory mediators released into the circulation and the distant effects of the disordered physiology of one organ on others, mediated either directly (i.e. hypoperfusion in cardiac failure) or indirectly, via pathophysiological neuro/endocrine effects. Concepts of cross-talk in MODS first gained a high level of interest in the setting of lung injury, where the generation of circulating inflammatory mediators from the large surface area of injured pulmonary epithelium was described as causing multi-organ dysfunction in distant organs, such as the kidney, cardiovascular system and gastrointestinal tract mediating the high mortality associated with adult respiratory distress syndromes (Imai et al. 2003). Importantly, in this context mediators might arise both as a consequence of the primary lung injury or secondary to effects of mechanical ventilation necessary to treat the primary respiratory failure (Husain-Syed et al. 2016). Similarly, isolated acute kidney injury caused by ischaemia reperfusion has been shown to mediate an inflammatory response that can result in secondary lung injury (Klein et al. 2008; Rabb et al. 2009), potentially setting up a vicious cycle of organ injury (**Figure 2**). In addition to the lung and the kidney the gastrointestinal tract may play a key role in the development of MODS, primary or secondary gastrointestinal injury from ischaemia, venous congestion or inflammation, as well as chronic effects of portal hypertension or uraemia, and may predispose to bacterial translocation and the systemic release of potent pathogen associated molecular patterns (Ko et al. 2009). In contrast, more physiological mechanisms of pathological organ cross-talk have been best described in the various forms of cardio-renal syndromes (Ronco et al. 2008), which reflect the effects of acute or chronic effects of cardiac dysfunction on the kidney and vice versa. These embrace forward and backward effects of cardiac dysfunction on the renal circulation, neuroendocrine abnormalities in acute and chronic cardiac and renal failure and, in particular, the deleterious effects of fluid overload on both organ systems. Inflammatory mechanisms also play a role in renal-cardiac interactions, for instance the pro-inflammatory milieu of chronic kidney disease. More recently, the cardio-renal model has been extended to reflect the interdependence of the heart, lungs and kidneys in cardio-renal-pulmonary syndromes (Husain-Syed et al. 2015). However, while these syndromes are very useful constructs for classifying mechanisms of illness, it remains questionable if forcing individual patients with complex and evolving illness into complex categorisations of

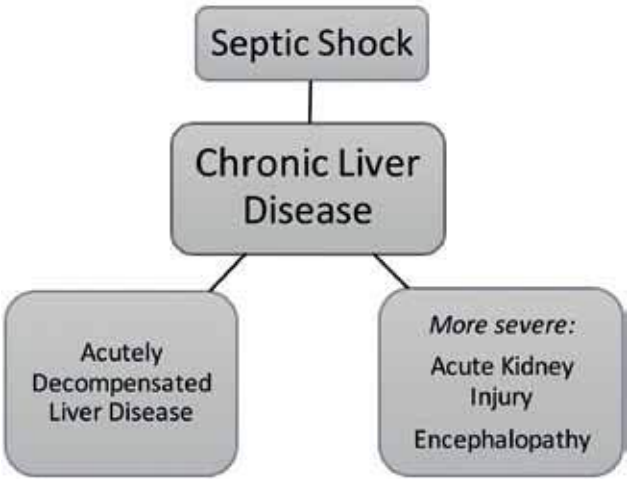

Figure 3. Example of the modifying effect of chronic organ dysfunction on increasing severity of primary and secondary organ injury

In this case of chronic liver disease multiple mechanisms will be involved including portal hypertension, gut translocation, circulating inflammatory mediators and pathophysiological activation of neuroendocrine responses.

acute and chronic multi-organ syndromes is useful to the treatment of the individual at the bedside.

An alternative to the development of complex classification of constellations of organ dysfunctions has been a focus on the role of individual organs as orchestrators of cross-talk. In the literature the kidney has been best described in this role due to its function in regulating fluid status, electrolytes and acid base and as a clearing house for many circulating low molecular weight inflammatory mediators, or conversely as a rich source of such mediators in injury (Doi and Rabb 2016; Grams and Rabb 2012). Furthermore the distant organ effects of chronic kidney disease are well recognised as leading to multi-system chronic disease. However, in the right context almost any organ system plays a central role in the development of MODS and, to some extent, the emphasis on a single organ is against the concept of organ cross-talk as a term encompassing the inter-dependent effects of many organs injuries.

How then does the clinician get through the diverse and complex process that comes under the umbrella of organ cross-talk to develop insights that are useful at the bedside? Firstly, active intervention to alter the course of established MODS with multiple mechanisms of cross-talk is likely to be very difficult due to the diversity of pathways driving this process and the potential for intervention directed at any organ to adversely affect others. Early recognition of the deteriorating patient, particularly in the context of established chronic organ disease is essential to preventing secondary organ injury and progressive organ dysfunction. Secondly, while multiple interdependent mechanisms of organ cross-talk are difficult to dissect there may be some key mediators of organ interaction that could be amenable to intervention or prevention, such as the systemic effects of fluid overload. Rather than trying to classify primary and secondary organ dysfunctions it may be better to identify the presence of unifying mechanisms of cross-talk that could be targeted for intervention. Finally we must not neglect the adverse effects of our therapies. If any lessons can be drawn from the last 30 years of critical care research, it is that targeting a specific physiological parameter in a single organ system is rarely beneficial, and more often harmful, and that in the treatment of the critically ill most often "less is more." As mechanisms of organ dysfunction in critical illness are complex and we are unlikely to fully understand any patient's illness at a given moment in time, we should resist the temptation to invoke rigid classifications of illness, but instead serially evaluate the clinical condition and response to treatment, seeking opportunities to assess the effects of interventions that may break cycles of organ dysfunction. The nature of such interventions will be crucially dependent on the clinical context. For instance, at one stage of illness appropriate fluid management could constitute resuscitation and, at another, fluid removal. Similar considerations of timing and context are likely to apply to anti- and pro-inflammatory interventions targeting humoral mechanisms of cross-talk. While targeted intervention to lessen pathological organ cross-talk holds great promise, in practice it is likely to be very challenging and will require careful patient characterisation.

Conflict of interest

John R. Prowle has consultancy agreements with Medibeacon Inc, Quark Pharmaceuticals Inc, GE Healthcare and Nikkiso Europe GmbH. Dr. Prowle has received speakers' fees and/or hospitality from Baxter Inc, Nikksio Europe GmbH and Fresenius Medical Care AG. ■

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POCUS and SHOCK

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Point-of-care ultrasound (POCUS) is an invaluable tool to differentiate the various types of shock which may co-exist in the critically unwell patient. It is beyond the remit of this article to teach the skill of POCUS. Rather, it provides an overview of how the various POCUS modules could be integrated and utilised in the shocked patient.

"A fool with a tool is still a fool"
Grady Brooch

What is point-of-care ultrasound?

Point-of-care ultrasound (POCUS) describes the use of ultrasound to extend the physical examination of patients at the bedside, guiding diagnosis and management. POCUS covers an array of ultrasound modules, including echocardiography, lung ultrasound, abdominal ultrasound etc.

The use of ultrasound has undeniably extended far beyond the walls of the radiology department, being utilised in more acute medical specialties such as emergency medicine and critical care. POCUS scans are different from those performed by radiologists or sonographers. These scans tend to be take place at the bedside in non-acute situations and are requested to answer very specific, detailed questions. POCUS scans are performed in order to answer questions, usually in a binary way i.e. yes or no. For an overview of POCUS and critical care, there has been a recent review in a previous edition of this journal (Zaidi and Koenig 2018).

There are numerous training resources available to clinicians, but crucially, the number of nationally-recognised accreditation programmes remains small. It is important to emphasise that clinicians must operate within their own competencies. The use of POCUS does not replace the need for thorough history taking, clinical examination and acumen. Instead, it enhances the clinician's ability to diagnose and manage critically ill patients. There is ongoing debate on whether POCUS will replace the stethoscope (Wittenberg 2014).

POCUS in shock – an integrated approach

Encountering the shocked patient is a common occurrence in the ED and the intensive care unit (ICU). Other articles in this issue have already covered the definition and types of shock. It must be emphasised that different types of shock may co-exist in the same patient e.g. the septic patient may be shocked due to distributive/vasodilatatory shock or cardiogenic shock. POCUS allows the clinician to more accurately identify the type and/or coexistence of the different types of shock and hence target management strategies accordingly.

> **"enhances the clinician's ability to diagnose and manage critically ill patients"**

A perceived weakness of comprehensive radiology or echocardiography scans is that they are often performed in isolation. As mentioned above, POCUS is performed by the bed space and the key to making these diagnoses is the ability to examine clinically, followed closely by ultrasound.

The key modules in the diagnosis and management of shock are the examination of the cardiovascular and respiratory system i.e. heart and lungs.

Focused echocardiography is probably the most established POCUS module. The key questions to be answered are:

- Is the left ventricle (LV) dilated or impaired?
- Is the right ventricle (RV) dilated or impaired?
- Is the inferior vena cava (IVC) collapsing?
- Is there a pericardial effusion?
- Is/are there pleural effusion(s)?

The complexity of the examination and the techniques used are obviously operator-dependent. However, there is broad consensus that basic transthoracic echocardiography should be a core competency for every critical care clinician.

Despite being a relatively new module, lung ultrasound has expanded exponentially since the work of Lichtenstein and colleagues (Lichtenstein and Mezière 2008). Once used only to assess for pleural effusions, superior to chest radiographs, our understanding and hence utilisation of this module has expanded to include a much broader range of diagnoses. A recent systematic review and meta-analysis concluded that lung ultrasound was superior to chest radiographs in terms of sensitivity, with similar specificity, hence challenging it as a first-line diagnostic tool (Winkler et al. 2018).

The Rapid Ultrasound for Shock and Hypotension (RUSH) protocol (Perera 2010) was designed so that emergency physicians could carry out a structured, easy-to-perform ultrasound examination (under two minutes). It requires an examination of the heart, intravascular filling status and large arteries/veins or simply Pump, Tank and Pipes respectively. **Table 1** summarises the ultrasonographic findings for the various types of shock using RUSH. As mentioned, it must be remembered that the various types can co-exist in the same patient.

The RUSH protocol is by no means the only integrated POCUS-based protocol; others include the SESAME (abbreviated from SESAMOOSIC Sequential Echographic Scanning Assessing Mechanism or Origin of Shock of Indistinct Cause) (**Figure 1**, Lichtenstein and Malbrain 2015) and the Abdominal and Cardiothoracic Evaluation with Sonography in Shock (ACES) protocols. Such integrated approaches form a significant part of most POCUS curricula and courses in emergency medicine and critical care.

In addition to its diagnostic prowess, POCUS can also be used to assess response to therapy such as fluid administration in the context of the shocked patient. Dynamic measures such as the velocity-time integral measured in the aortic outflow tract have been shown to be a useful measure of fluid responsiveness (Miller and Mandeville 2016).

Integrating POCUS into daily practice

POCUS, like any other monitoring device, has not been shown to improve patient outcomes without being coupled with an appropriate management strategy. The recently published SHoC-ED trial (Atkinson et al. 2018) failed to show any mortality benefit when shocked patients were managed using a POCUS-centric approach compared to standard care. The reasons are probably multifactorial, but this should act as a word of caution to the enthusiastic practitioner.

The best time to perform a POCUS examination is when the patient requires it. The convenience does come at the cost of taking up clinician time and interrupting the workflow of the day and ward round; this interruption is particularly relevant since not all clinicians are currently competent in POCUS. With clinicians' time increasingly being stretched, a way of balancing the inherent benefits of POCUS and drawbacks is crucial. Ultimately, different ICUs adopt different techniques based on staffing, working shift patterns, experience and availability of POCUS practitioners, number of ICU/ high dependency unit (HDU) beds, workload and ready access to a suitable ultrasound machine. There is unlikely to be a single best method and the most practical and realistic way of incorporating POCUS into the working culture, training and patient care on the ICU is probably a combination of all three.

Table 1. Summary of findings of RUSH examination in types of shock

	Hypovolaemic shock	Cardiogenic shock	Distributive shock	Obstructive shock
Pump	Hyperdynamic heart	Poor contractility	Hyperdynamic heart (early sepsis) Poor contractility (late sepsis)	Pericardial tamponade RV strain Poor contractility
Tank	Small, collapsing IVC Peritoneal or pleural fluid	Large, non-collapsing IVC B-line profile in lungs Pleural effusion	Normal/small IVC Pleural or peritoneal fluid	Large, non-collapsing IVC Absent lung sliding
Pipes	Ruptured Abdominal Aneurysm or Dissection	Normal	Normal	DVT

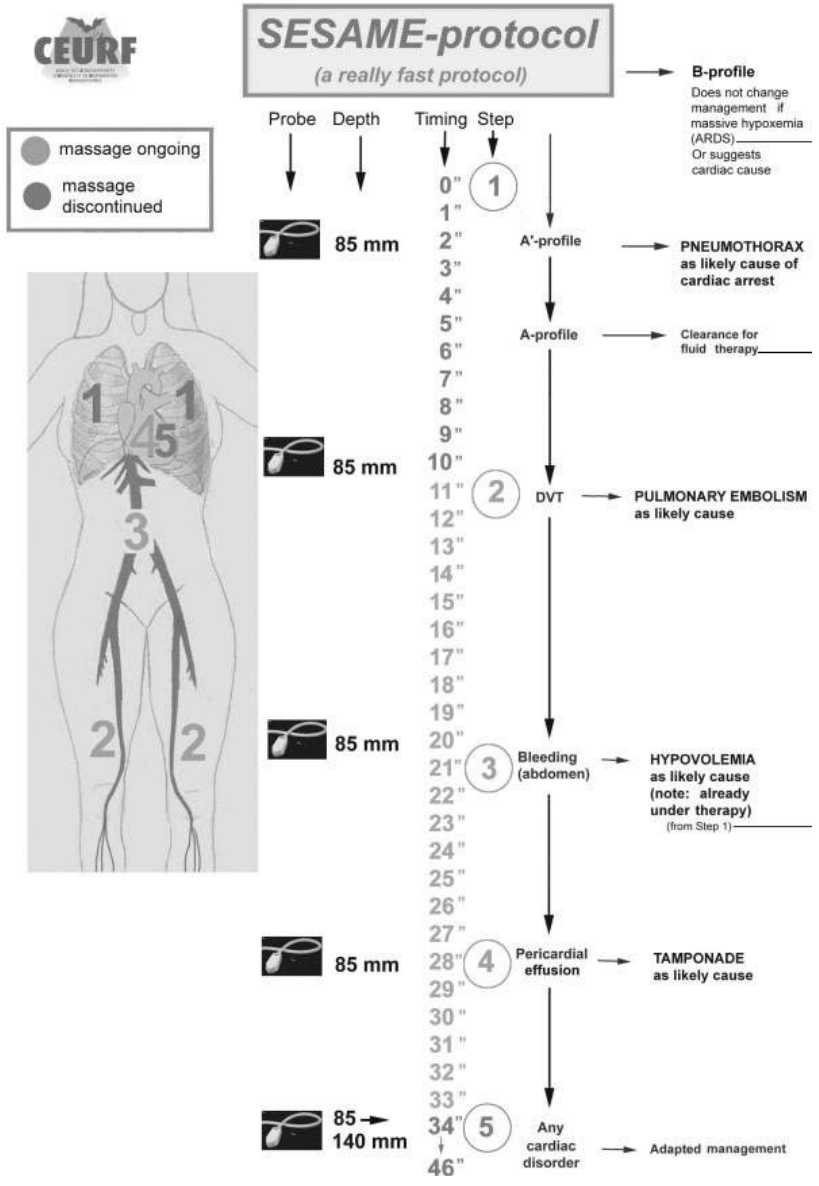

Figure 1. SESAME protocol

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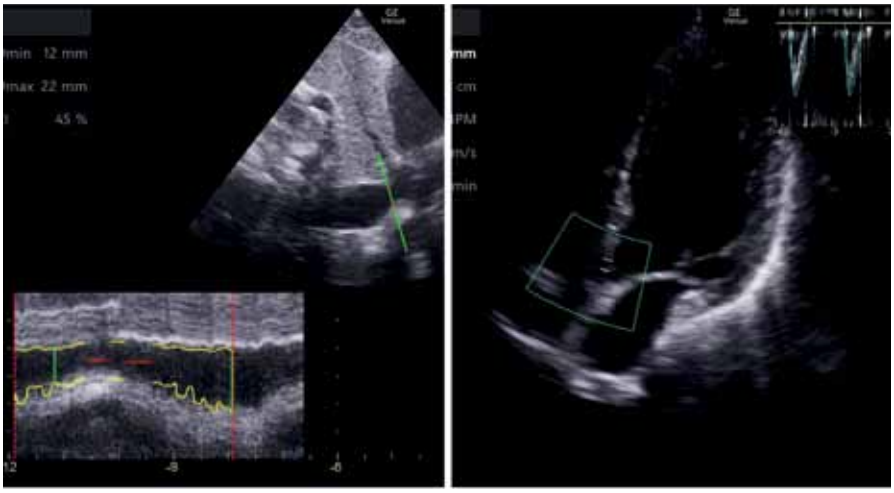

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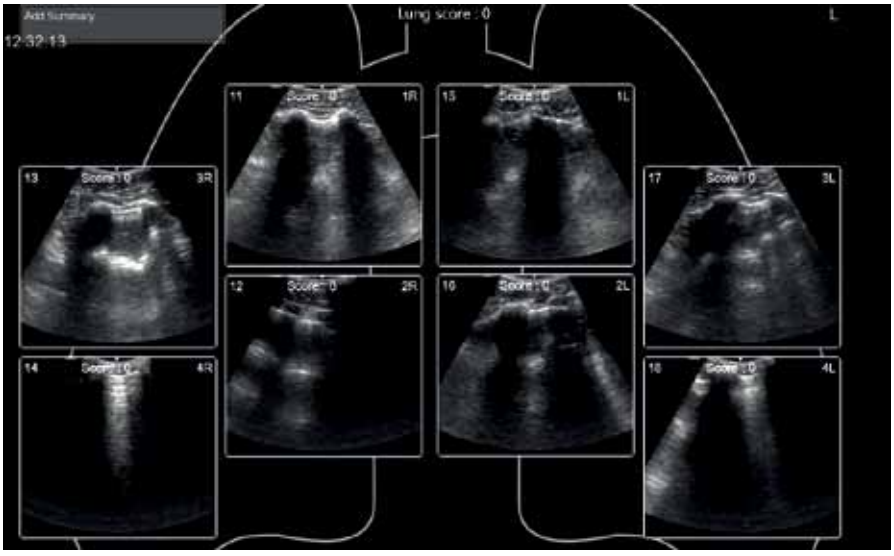

Figure 3.

What the future may hold

There is broad consensus that basic POCUS should be part of core competencies for intensivists. Consensus and expert statements published in 2011 (Expert Round Table on Ultrasound in ICU 2011) have led to the development of national accreditation programmes to support colleagues in developing and maintaining this skillset. Comparisons of these programmes highlight a degree of variability between them and consensus is needed to better define these competencies to ensure high-quality training and ultimately improve patient care.

Supporting improved access to training, technology continues to advance in order to make POCUS machines more accessible and portable. Earlier ultrasound machines were often bulky, not very portable and were considered cumbersome to use. The newer machines of several manufacturers can now fit into the palm of your hand e.g. Philips Lumify™ and Sonosite IVIZ™. Some of these probes are plugged into the clinician's smartphone and utilise the screen of the device. Early versions of such portable ultrasound machines had variable image quality and functionality as a trade-off to size but again, more modern devices have closed this gap.

Image acquisition is only one part of the ability to make the diagnosis and formulate a management plan. Image interpretation is an integral part of the training process and competency assessment. Artificial intelligence (AI), as seen in other industries has also started to 'invade' healthcare. Several manuscripts on the use of AI to interpret scans for signs of malignancies have been published. Extrapolating from this example, machines such as the GE Venue™ have built-in software in order to facilitate measurements of cardiac output and interpret lung ultrasound findings (**Figure 2 and 3**). These AI systems are meant to aid and not replace the human clinician.

Conclusion

Shock is a common, complex clinical condition with several classical types that may co-exist. POCUS techniques offer a powerful diagnostic and management tool which is within the skillset of intensivists after appropriate training. ■

Conflict of interest

Adrian Wong and Jonathan Wilkinson have both trialled various ultrasound devices from different manufacturers. JW has self-funded a portable ultrasound device for his own personal use in his clinical work. AW and JW declare that they have no financial conflict of interest.

Abbreviations

ICU intensive care unit
POCUS point-of-care ultrasound

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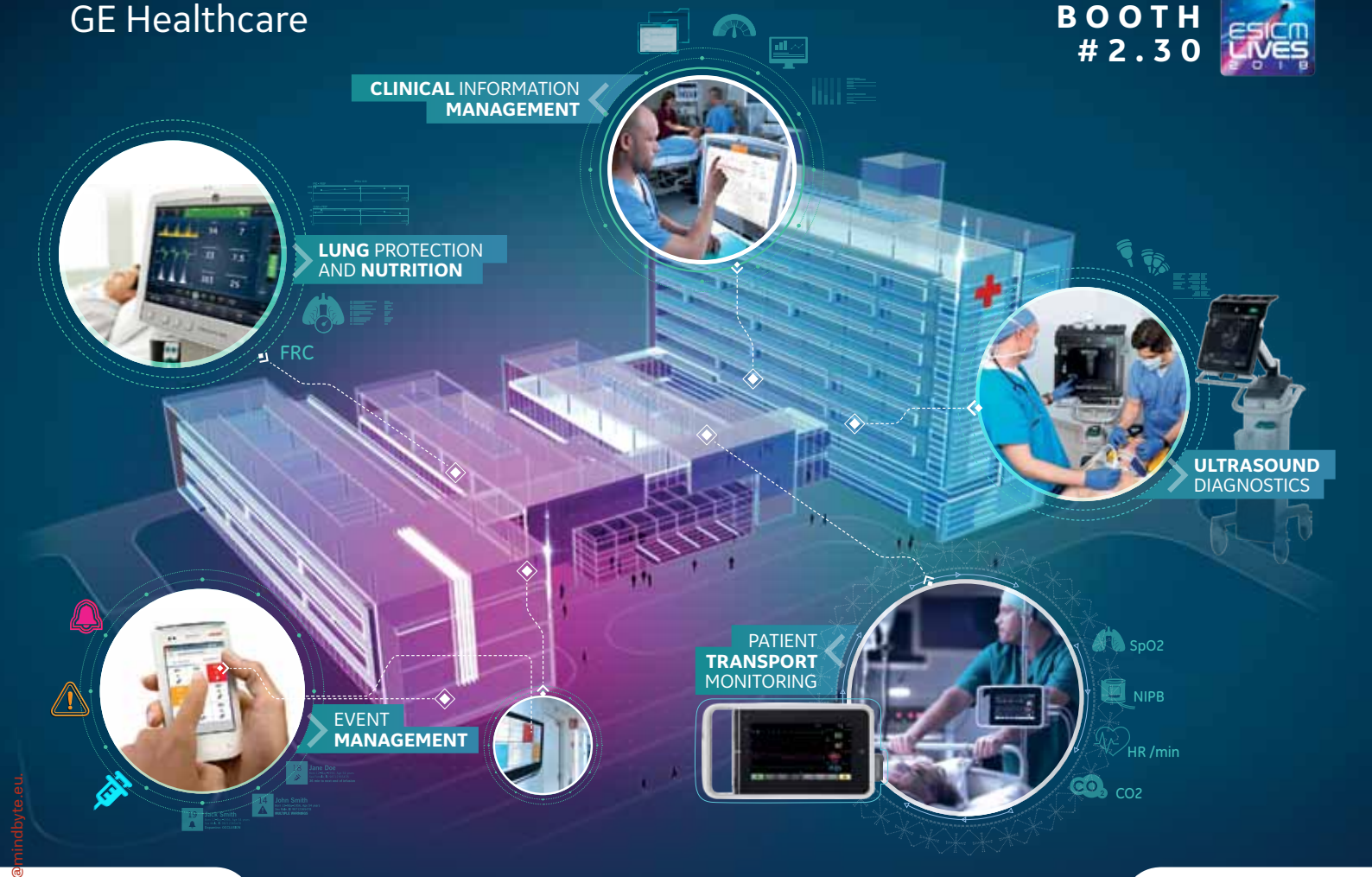

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  Prof. Erwan L'HER (Brest, France)
- Big data and Analytics as support tools to capitalize on practice?
  Dr. Erik KOOMEN (Utrecht, Netherlands)
- Speed-up clinical decisions using Ultrasound and Artificial Intelligence.
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Key decisions in a goal-directed coagulation management approach

An individualised goal-directed approach to managing coagulopathy is recommended to treat bleeding trauma patients.

Severe trauma is a great burden to society, with millions of victims worldwide. If trauma patients are hazardly bleeding, surgical bleeding requires the surgeon to fix the problem, while coagulopathy requires management with an algorithm that includes monitoring and specific treatment. About 30% of all major trauma patients have a significant coagulopathy at hospital admission (Maegele 2010).

In most trauma patients low fibrinogen concentration is a key element of their coagulopathy. Fibrinogen is central to the coagulation system as it is vital for platelet aggregation and a key substrate of plasmatic coagulation (Spahn et al. 2013). Fibrinogen is the coagulation 'element' that becomes critically reduced first in many clinical situations, including trauma. The critical level of fibrinogen may be < 1.5-2.0g/L or a maximum clot firmness (MCF) in FIBTEM of < 7mm, or even < 10mm, as measured by a point-of-care rotational thromboelastometry (ROTEM) device.

Unlike red blood cells (RBCs) and platelets there are no fibrinogen stores in the body that might be mobilised. When bleeding lasts a long time and lost volume is replaced with crystalloids and/or colloids, haemoglobin goes down exponentially. At a certain stage it does not go down anymore despite ongoing blood loss, because RBCs are mobilised. Platelets can also go down, but they can be stabilised or increased at a later stage since also platelets can be mobilised. This is not the case for fibrinogen. The more bleeding is ongoing the more likely the need to replace fibrinogen with exogenous fibrinogen.

Fibrinogen replacement

Fresh frozen plasma

A systematic review of randomised controlled trials using fresh frozen plasma (FFP) concluded that for most clinical situations the evidence for clinical efficacy is limited (Stanworth et al. 2004). FFP is an important source of factor V in demonstrable multi-factor deficiency with severe bleeding (Stanworth et al. 2004), but there is limited data on use in liver bleeding. Guidelines state that whether and how much FFP to use to treat a patient with massive blood loss should be guided by timely tests of coagulation, including near-patient tests. Formulae to guide replacement strategies should not be used (Stanworth et al. 2004).

FFP transfusions are associated with major adverse outcomes, including increased mortality (Welsby et al. 2010), increased multi-organ failure (Watson et al. 2009), increased infection (Sarani et al. 2008), increased transfusion-associated lung injury (TRALI) (Silliman et al. 2005; Rana et al. 2006; Eder et al. 2007; Chaiwat et al. 2009), transfusion-associated circulatory overload (TACO) (Rana et al. 2006) and, most importantly, inefficacy in treating coagulopathy (Weber et al. 2012; Innerhofer et al. 2017; Stein et al. 2017a).

The more bleeding there is, the more likely the need to replace fibrinogen from other sources to achieve a minimum fibrinogen concentration of 1.5 to 2 g/L. Sources of fibrinogen are FFP, fibrinogen concentrate and cryoprecipitate. The range of fibrinogen concentration in FFP is 1 to 3 g/L, and is highly variable between units (Levy and Goodnough 2015).

Pathogen inactivation reduces fibrinogen concentration further and consistently to a concentration below 2g/L. If several units of FFP are transfused at a time a vicious cycle starts (**Table 1**).

Fibrinogen replacement therapy

There is guidance on how to use fibrinogen replacement therapy in acquired bleeding (Levy and Goodnough 2015; Theusinger et al. 2017; Garrigue et al. 2018).

Fibrinogen concentration measurement

In a goal-directed approach to coagulation management, it is essential to measure and monitor fibrinogen concentration. However, laboratory measurement of fibrinogen concentration is difficult. Solomon et al. (2014) showed that six laboratories had differences of fibrinogen concentration measurements of 80% between them for 30 patient samples, before, during and after cardiopulmonary bypass. The first international standard established by the World Health Organization for fibrinogen concentrate is 10.4 g/L (National Institute for Biological Standards and Control 2008); the results in this study varied from 2-12 g/L. In addition, the laboratory value takes at least 30 to 60 minutes to reach the doctor ordering the test.

Table 1. Clinical consequences of fresh frozen plasma administration

Fibrinogen concentration → or ↓
Haemoglobin concentration ↓ and platelet count ↓
→ coagulopathy
RBC transfusion
Coagulation potential ↓
Further FFP administration - triggers a vicious cycle

Therefore, it is best to base the coagulation algorithm on a ROTEM or thrombelastography (TEG) monitoring device. In 10 minutes there is a clear answer if there is something wrong with the coagulation and what is wrong. There are concerns that this technology is expensive. However, the UK National Health Service found consistent cost savings in viscoelastic point-of-care testing compared with standard lab tests to assist with diagnosis, management and monitoring of haemostasis in cardiac surgery and particularly trauma (Whiting et al. 2015). Their systematic review of 31 trials (11 in cardiac surgery with 1089 patients) showed reduction in blood product use [RBC RR 0.88 (0.80-0.96); FFP RR 0.47 (0.35-0.65)] and platelets RR 0.72 (0.58-0.89). And it is efficacious. A prospective study that randomised patients after heparin reversal following cardiopulmonary bypass compared coagulation management based on conventional laboratory analyses with two algorithms, intra- and postoperative, based on ROTEM. The ROTEM group received fewer RBCs and did not receive FFP; platelets were about the same, fibrinogen usage was the same, there was no rFVIIa anymore and the cost of haemotherapy (including cost of monitoring, blood products and factor concentrate) was about half. The patients in the ROTEM group had better survival at 6-months (Weber et al. 2012).

Some have suggested that practice in trauma patients should be based on the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, believing that it proved that 1:1:1 (platelets:FFP:RBC) is better than 1:1:2 (Holcomb et al. 2015). However, the primary outcome, 24h-30 day mortality, was similar between the two formulae. Nascimento et al. (2013) showed that a 1:1:1 ratio is inferior to a control group treated based on a laboratory-based algorithm.

The European guideline on management of major bleeding and coagulopathy following trauma recommends that routine practice includes early and repeated monitoring of coagulation, using either a traditional laboratory determination of fibrinogen concentration [prothrombin time (PT), activated partial thromboplastin time (APTT) platelet counts and fibrinogen] and/or a viscoelastic method (ROTEM or TEG) (Rossaint et al. 2016). Measurement is required after each treatment to ensure that fibrinogen remains.

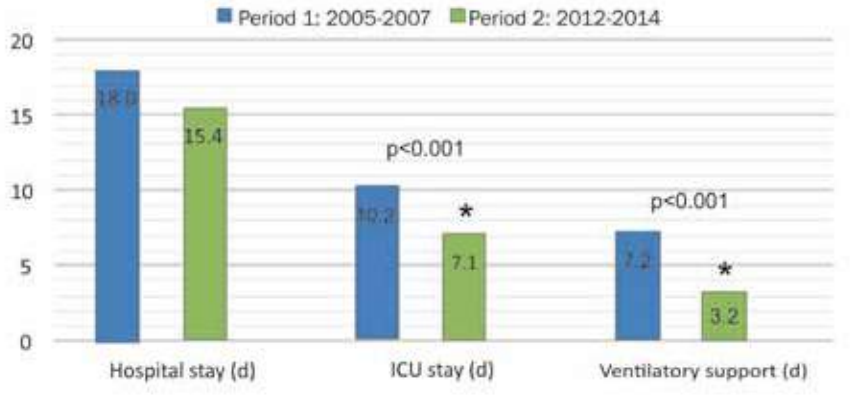

Figure 1. Outcome of patient cohorts managed traditionally (2005-2007) and with coagulation algorithm (2012-2014) (Stein et al. 2017a)

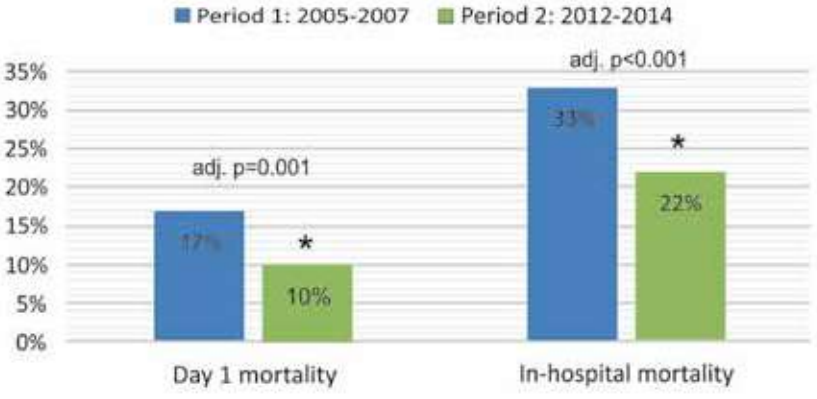

Figure 2. Mortality of patient cohorts managed traditionally (2005-2007) and with coagulation algorithm (2012-2014) (Stein et al. 2017a)

Tranexamic acid

The European guideline recommends that tranexamic acid be administered as early as possible to the trauma patient who is bleeding or at risk of significant haemorrhage at a loading dose of 1g infused over 10 minutes, followed by an IV infusion of 1g over 7 hours (Rossaint et al. 2016).

In a prospective, multicentre observational study (*TXA in the EMS on the Helicopter and the Ambulance*, NCT 02354885), our group gave 1g of tranexamic acid intravenously early on scene to 70 trauma patients (Stein et al. 2018). The control group (n=38) did not receive tranexamic acid. The coagulation of these control patients deteriorated until hospital admission. In contrast, patients who received tranexamic acid on scene had clot stabilisation on arrival at the emergency department (ED). There were four cases with documented hyperfibrinolysis on-scene in the tranexamic acid group; in all these cases there was no sign of hyperfibrinolysis detectable at hospital admission.

Therefore, 90 minutes after the initial dose of 1g tranexamic acid re-dosing is required with an individualised goal-directed strategy to keep the fibrinogen level to a minimum of 1.5 to 2.0 g/L.

In a recent prospective multicentre observational study in major trauma patients receiving tranexamic acid on scene, plasma concentration was measured at hospital admission (Grassin-Delyle et al. 2018). The study authors propose a dosing scheme to maintain a specific target blood concentration.

The European guidelines recommend treatment with fibrinogen and cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less

Table 2. Coagulation algorithm

Detect low fibrinogen	
MCF in FIBTEM ≤ 7mm	Fibrinogen 2-4 g IV (after 6 g of fibrinogen, administer Factor XIII 15 U/kg IV)
Detect fibrinolysis	
EXTEM/INTEM: Clot lysis after MCF and APTEM: normal = hyperfibrinolysis	Tranexamic acid • Bolus: 15 mg/kg IV (consider empiric use) • Consider continuous infusion 1-2 mg/kg/h
Ongoing bleeding	
Factor XIII < 60%	Factor XIII 15 U/kg IV
Platelet count/function • EXTEM/INTEM MCF < 40mm • Platelet count ≤ 50,000/µl (≤ 100,000/ µl in cardiac surgery or traumatic brain injury)	Platelet concentrate
• Platelet function (impedance aggregometry)	Consider desmopressin 0.3 µg/kg (max 16 µg) in case of aspirin (like) platelet dysfunction
• INR > 2.3 (Quick's value < 30%)	Four-factor prothrombin complex concentrate (slow continuous infusion of small repeated doses - e.g. 500 IU)
• Factor V < 20%)	FFP (2-4 units)
Detect heparin	
INTEM (CT/CFT) or ACT prolonged and HEPTEM or heparinase-ACT normal	Protamine (1:1) to antagonise heparin

Source: Stein et al. 2017b

than 1.5-2.0 g/L (Rossaint et al. 2016).

Some express caution over giving fibrinogen to patients as it may induce higher than normal plasma fibrinogen levels after major trauma. However, in their study of the time course of plasma fibrinogen, Schlimp and colleagues (2016) showed that fibrinogen concentrate treatment at admission does not lead to higher fibrinogen, concentration levels post-trauma beyond that occurring naturally due to the acute phase response.

Prothrombin complex concentrate

The European guidelines recommend early use of prothrombin complex concentrate (PCC) for the emergency reversal of vitamin K-dependent oral anticoagulants (Rossaint et al. 2016).

One study showed that using four-factor PCC compared to plasma had much faster vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions (Goldstein et al. 2015), which is key in traumatised patients. PCCs are also indicated according to the European guidelines, if there is evidence of delayed initiation of coagulation using viscoelastic monitoring (CT in EXTEM), but the condition is that fibrinogen has been normalised. Therefore, we normalise fibrinogen first and give PCCs only if the CT remains elevated after fibrinogen administration.

Coagulation algorithm

Traditional management of coagulopathy was compared with an individualised goal-directed coagulation and transfusion protocol during two time periods (Stein et al. 2017a). During the first period (2005-2007) we used traditional management and in the second period (2012-2014) a protocol that included primary whole-body CT, tranexamic acid, restrictive fluid therapy (preferably crystalloids), permissive hypovolaemia/hypotension and damage control surgery, according to the European guidelines. The outcome was the comparison between the observed and the Trauma Associated Severe Haemorrhage (TASH)-predicted massive transfusion rate to ICU admission. The simple coagulation algorithm is shown in **Table 2** (Stein et al. 2017b).

In the second period the goal-directed protocol resulted in half the expected massive transfusion rate predicted, the same platelet count and fibrinogen, more tranexamic acid and no rFVIIa (Stein et al. 2017a). ICU length of stay (LOS) was reduced by 3 days, ventilatory support reduced by 4 days (**Figure 1**). Also mortality was reduced (**Figure 2**). ■

Abbreviations

FFP fresh frozen plasma
MCF maximum clot firmness
PCC prothrombin complex concentrate
RBC red blood cells
ROTEM rotational thromboelastometry
TEG thromboelastography

Key Points

- Fibrinogen is the coagulation element that becomes critically reduced first in many instances
- In trauma and cardiac surgery patients, the critical level is 1.5 to 2.0 g/L
- Immediate viscoelastic coagulation monitoring is key for individualised goal-directed coagulation algorithms
- Coagulation algorithms should be available in every hospital
- Compliance with the European trauma treatment guidelines improves survival

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Evidence for using first-line coagulation factor concentrates for trauma-induced coagulopathy

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Fibrinogen limits coagulopathy and massive bleeding, has less transfusion requirements and thereby decreases the risk of multi-organ failure in trauma patients.

What stops the bleeding?

Haemostatic therapy aims to stop the bleeding, but is it a concentration of coagulation factors, mainly assessed by international normalised ratio (INR) readings that works, or is it fibrinogen/fibrin, which are the precondition for stable clot formation? We conducted a study in patients with polytrauma and those with isolated brain injury (Tauber et al. 2011) to find out what the most predominant pathology was (**Figure 1**). The red bars refer to polytrauma patients. There is significant increase in the frequency of low fibrinogen, low fibrinpolymerization and consequently low clot firmness, in 20-30%, while a significant and prolonged INR of about 1.5 was found in only about 14%. Clot firmness and fibrin polymerization were independently associated with mortality and also with blood loss as measured by early transfusion requirements. In addition patients had tremendously increased molecular markers of thrombin generation, regardless of the INR readings. It's not the main interest to increase it more by substituting plasma, because very huge thrombin levels do not benefit trauma patients. It may cause endothelial injury and also activate other receptors and inflammation and so on.

Further results confirm these findings, e.g. in a study that included more than 4,000 patients, with injury severity scores (ISS) considerably lower than in our patient population, fibrinogen deficiency occurred frequently and fibrinogen levels < 1.5g/L were associated with increased mortality (McQuilten et al. 2017). Hagemo et al.'s study investigating 1,133 patients in a multicentre trial, found that increased mortality was associated with fibrinogen levels < 2.29 g/L, which is barely below normal (Hagemo et al. 2014). The INR was not independently associated with mortality.

Coagulation factor substitutes

Plasma

Plasma refers to 6-8% protein solution and 92-94% water. It was introduced in clinical practice mainly for volume substitution but later to treat coagulation disorders. It contains all procoagulants and also anticoagulants. It's easy to use, is considered safe regarding thrombosis, and relatively low-cost. However, plasma transfusion is time-consuming and requires planning.

The concentration of coagulation factors and especially fibrinogen are rather low in plasma and vary depending on the individual donor and the type of processing. Plasma efficacy can be questioned and partial requirements correction is not possible. It may also induce transfusion-associated circulatory overload (TACO), transfusion-associated lung injury (TRALI), transfusion-associated immunomodulation (TRIM), multi-organ failure (MOF), immunosuppression, lung injury.

Fibrinogen concentrate

There are several concentrates on the market:

1. Fibrinogen concentrate
2. FXIII concentrate
3. PCC (FII, VII, IX, X)
4. vWF concentrate
5. rVIIa, PCCa
6. FVIII, IX, X, XI concentrate

No factor V concentrate is available.

Concentrates are immediately ready to use, contain defined and high concentration of the factor, no volume expansion is needed,

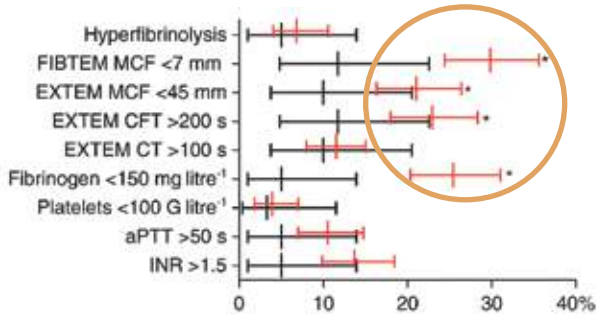

Figure 1

Source: Tauber et al. (2011)

so there will be an effective rise in concentration, making targeted therapy possible. There will be no TACO, TRALI or TRIM and the concentrates are virus-inactivated.

The main problem is cost; they are more expensive than plasma. Some may be concerned about the risk of thromboembolism, and this may occur if thrombin formation is increased by use of PCC and activated PCC and rFVIIa. It is not a problem with fibrinogen, which is also called antithrombin I, as fibrinogen and fibrin are able to capture free-flowing thrombin, and thrombin is the one that initiates thrombosis. Authors of reviews and meta-analyses also criticise the fact that currently there are only a few high-quality studies in trauma patients showing a benefit with coagulation factor concentrates.

The European guideline (Rossaint et al. 2016) recommends the use of standard coagulation tests and/or viscoelastic tests (level of evidence 1C). Viscoelastic testing gives a timely and more comprehensive picture. The guideline recommends use of plasma together with RBC at least 1:2 or use of fibrinogen concentrate with RBC and PCC and factor XIII in selected cases.

Evidence for fibrinogen concentrate

The most frequently cited studies using coagulation factor concentrates in trauma patients are summarised in **Table 1**. All show promising results: lower mortality than predicted, lower transfusion requirements, and lower multi-organ failure. Fibrinogen was maintained within a normal range even if much fibrinogen had been administered. There were fewer transfusions of red blood cells (RBCs) and platelets. In the study by Wafaisade and colleagues (2013), early mortality was also reduced. These patients received fibrinogen and also had massive transfusions of plasma.

Meta-analyses on plasma efficacy in bleeding patients have concluded that there is no clear benefit for blood loss, transfusion and mortality (Stanworth et al. 2004; Casbard et al. 2004; Yang et al. 2012; Kozek-Langenecker et al. 2011; Desborough et al. 2015). However, there are several reports in trauma patients showing improved survival with early aggressive transfusion without any blood measurements. Administration of 1:1 ratios is recommended, but there are studies that found that mortality did not change and coagulopathy was not corrected (**Table 2**). Before massive transfusion of plasma, reported mortality in many centres was about 50 percent. Now the rate is between 21% and 35% (**Table 3**). This mortality is considerably higher than studies using a targeted correction of coagulopathy and using coagulation factor concentrates, especially fibrinogen concentrate.

RETIC trial comparing plasma and coagulation factor concentrates

Our study group conducted the first randomised controlled trial comparing the effect of a plasma-based strategy to the use of coagulation factor concentrate in severe trauma (Innerhofer 2017). The study was

Table 1. Are CFCs useful in trauma patients?

Author	Design	n/ISS	Products	Main result
Schöchl 2010	Retrospective	131 38 ± 15	FC (128) PCC (98) FFP (12)	Mortality lower than predicted
Schöchl 2011	Retrospective	681 35 ± 11	CFC n=80 FFP n=601	Fewer RBC and PC with CFC
Nienaber 2011	Retrospective matched pair	311 44 (38,50)	CFC n=18 FFP n=293	Fewer RBC, lower MOF with CFC
Schlimp 2013	Retrospective	157 29 (23,41)	FC n=85 FC+PCC n=63 FC+PCC+FFP n=9	Fibrinogen maintained, within normal range at 24h ICU
Innerhofer 2013	Observational	144 37 (29,50)	CFC n=66 CFC +FFP n=78	Fewer RBC and PC with CFC alone, lower MOF
Wafaisade 2013	Retrospective matched pair	588 37 ± 13	FC 294 no FC 294	Reduced 6h mortality and MOF with FC

CFC coagulation factor concentrate FC fibrinogen concentrate FFP fresh frozen plasma MOF multi-organ failure PCC prothrombin complex concentrate RBC red blood cells

Table 2. Massive transfusion: Fixed ratio RBC: FFP: PC

Pro 1:1		Indifferent		Con	
Study	Type	Study	Type	Study	Type
Hirshberg et al. 2003	Mathematical model	Rangarajan et al. 2011	Retrospective	Scalea et al. 2008	Prospective
Maegele et al. 2008	Retrospective	Dirks et al. 2010	Retrospective	Nienaber et al. 2011	Matched pair analysis
Gonzalez et al. 2007	Retrospective	Magnotti et al. 2011	Registry - selection bias!	Johnson et al. 2010	Prospective
Duchesne et al. 2009	Retrospective	Snyder et al. 2009	Retrospective - selection bias!	Edens et al. 2010	Prospective
Teixeira et al. 2009	Retrospective	Holcomb et al. 2015	Only early death (secondary endpoint)	Kashuk et al. 2008	Prospective
Mitra et al. 2010	Retrospective			Rourke et al. 2012	Prospective
Peiniger et al. 2011	Retrospective			Chambers et al. 2011	Before/after
Holcomb et al. 2013	Prospective			Kahn et al. 2014	Prospective

Table 3. Mortality in trauma - 1:1:1(2) vs POCT-directed individualised therapy

Country	Author	Mortality	ISS
USA	Holcomb 2013	21.4-25.0%	25-26
USA	Nascimento 2013	24%	35 ± 13
USA	Holcomb 2015	24.3%	25
USA	Gonzalez 2016	27%	33 (25;43)
UK	Khan 2014	35%	34 (25;41)
Austria	Tauber 2011	12.8%	35 (25;50)
Austria	Innerhofer 2013	7.6%	37 (29;50)
Austria	Schöchl 2011	7.5-10%	35.5 ± 10.5
Austria	Innerhofer 2017	7.4%	34 (26;43)

terminated early following interim analysis after inclusion of 100 patients, because predefined stopping was met, showing disadvantages with use of plasma. Correction of coagulopathy was feasible in 96% of patients in the CFC group; only 2 patients had treatment failure and also received plasma (**Table 4**).

In the plasma group more than 50% of patients had no stop of bleeding and no correction of coagulation. These patients received additionally fibrinogen concentrate, some also PCC and factor XIII. Transfusion requirements were increased and patients received more frequently platelet concentrates. Importantly, the rate of massive transfusion at comparable ISS was increased tremendously.

Our primary endpoint was difference in MOF. However, to answer this question, we would have needed to include at least 200 patients. Therefore the difference of 16% between groups with a higher rate of MOF in the plasma group was not significant. However, ISS and brain injury are confounders, which should be considered when analysing the likelihood of MOF. These confounders were used for stratification and considered in regression analysis. Results showed a significant increased risk of MOF with plasma (OR 3·13 [1·19–8·88], p=0·025) even in this limited population of 94 patients.

What stops the bleeding–the concentration or the clot?

In the RETIC study the blue boxes refer to the CFC group that mainly received fibrinogen concentrate. The yellow boxes refer to the plasma group (**Figure 2**). Prothrombin is indexed as a percentage of normal, and at baseline they are comparable. After administration of plasma this improved, but decreased further in the CFC group. The patients in the plasma group received more RBC and platelets concentrates and, despite this, had a dramatic drop in platelet count. Also the haemoglobin levels were lower than in the CFC group that received fewer RBCS and platelets. Therefore improved INR or prothrombin time does not limit blood loss. What about fibrinogen and clot firmness? Fibrinogen increased to its normal levels immediately with the factor-based concept, but changed little and marginally and remained below normal in the plasma group. Consequently clot strength improved rapidly with CFC but remained unchanged or decreased in the plasma group. ■

Table 4. RETIC trial main findings

	CFC (n=50)	FFP (n=44)	OR	*P* value
Treatment failure (n)	2 (4%)	23 (52.3%)	25.34	<0.001
RBC/24h	4 (2.7)	6 (4,11)		.028
PC yes	20%	47.7%	3.599	.008
MT%	12%	29.5%	3.038	.042
MOF%	50%	65.9%		.1457

Logistic regression adjusted for confounders ISS/TBI
Significantly increased risk for MOF with FFP OR 3.1264 (CI 1.1906 - 9.8756), P = .0250

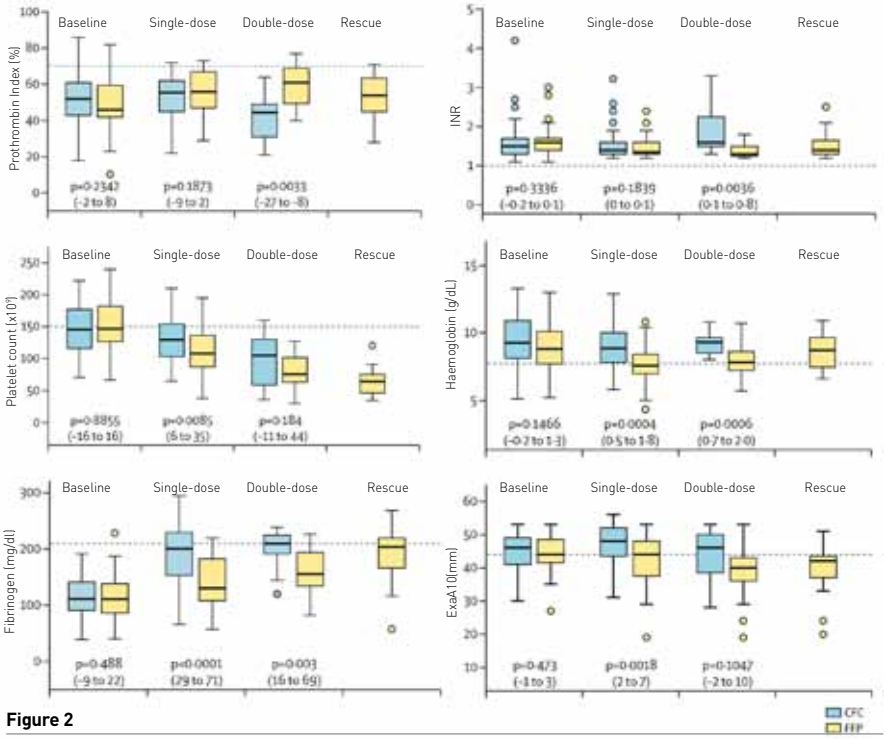

Figure 2

Abbreviations

ISS injury severity score
MOF multi-organ failure
TACO transfusion-associated circulatory overload
TRALI transfusion-associated lung injury
TRIM transfusion-associated immunomodulation

References

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Conclusion/ Key points

- Early and effective fibrinogen supplementation is really important to limit blood loss and minimise risk of MOF
- Fibrinogen improves clot strength and also exhibits a platelet-saving effect. This is very important because platelets are one of the transfusion components that are sometimes dangerous and have many side effects
- Fibrinogen limits coagulopathy and massive bleeding and has less transfusion requirements especially massive transfusion and thereby it also decreases the risk of MOF
- An effective rise of fibrinogen concentration is not feasible with plasma
- The lower, better INR after plasma does not reduce the bleeding, therefore we should not focus on the INR
- Fibrinogen is of interest, should be monitored and should be supplemented early

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Implementation of a revised trauma management protocol

Goal-directed therapy of coagulopathy is recommended for trauma patients.

Can guidelines direct our strategy?

When presented with bleeding trauma patients, our management strategy may be directed by guidelines, e.g. the European trauma guideline (Rossaint et al. 2016). This recommends treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/L. An initial fibrinogen supplementation of 3–4 g is suggested, and repeat doses must be guided by viscoelastic monitoring and laboratory assessment (Rossaint et al. 2016).

Guidelines are developed on a scientific empirical basis, but in clinical practice it can be hard to define which patient will bleed in the next 30 minutes with a clinically substantial bleed. The U.S. guidelines recommend 1:1:1 massive transfusion packages (American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015), which have the advantage of additional volume effect, but the disadvantages of side effects of fresh frozen plasma (FFP), time delay, prophylactic transfusion and lower efficacy. The European guideline recommends individualised targeted controlled coagulation management and transfusion, which requires point-of-care monitoring and administration of colloids/crystalloids to give additional volume. The advantages are that no prophylactic transfusion is required, there are fewer side effects of transfusion-related complications and it is efficacious.

Massive transfusion protocols: fixed ratios (1:1:1)

The evidence for a 1:1:1 (platelets:FFP:red blood cells [RBC]) ratio in transfusion is that it is not beneficial. Abdel-Wahab and colleagues showed in an audit of patients transfused FFP for mild coagulation values that prothrombin time (PT) was partially normalised in a minority of patients and did not correct the PT in 99 percent of patients, regardless of the number of units of FFP transfused (Abdel-Wahab et al. 2006). Concentration is not increased by transfusing FFP, which has a low concentration of coagulation factor.

Studies on 1:1:1 transfusions have a clear survivor/publication bias, as most studies in support came from war situations, when RBCs were available in 20 minutes and plasma within 90 minutes. The result was not that FFP saved the patient, but that the patients who survived at least the first 60-90 minutes were able to receive the plasma. For example, Snyder and colleagues (2009) found an association between higher FFP:packed red blood cells [PRBC] ratios at 24 hours and improved survival, which after adjustment for survival bias was no longer statistically significant. Manotti and colleagues (2011) analysed outcomes for trauma patients who received massive blood transfusion. Patients who received a higher plasma ratio during the first 24 hours had an improved survival rate, but were in less shock. The authors note: "The proposed survival advantage of a high-ratio may be because of selection of those not likely to die in the first place; that is, patients die with a low-ratio not because of a low-ratio."

A prospective cohort study of 517 trauma patients in whom FFP and RBCs were administered in fixed ratios found that fibrinogen was always low at admission, and they needed to administer cryoprecipitate to increase fibrinogen levels (Rourke et al. 2012). In patients with low fibrinogen at admission mortality was increased, while patients who received cryoprecipitate had improved survival.

Frith and colleagues (2015) analysed thrombin generation parameters in 440 trauma patients following FFP transfusion in a RBC:FFP:platelets ratio of 1:1:5. Both patients with and without acute traumatic coagulopathy had low thrombin generation after receiving four units. Both groups had a further 25% decline in thrombin generation during the next four units, so conventional haemostatic resuscitation failed to support the thrombin generation required for fibrinogen conversion.

Khan and colleagues, in an international prospective cohort study, drew a blood sample when trauma patients arrived at the hospital, and after 4, 8 and 12 PRBC transfusions in 160 patients. The percentage of coagulopathic patients went up the more transfusions were received (58% after 4 PRBC, 81% after 8) (Khan et al. 2015).

Nascimento and colleagues compared the effect of a fixed-ratio (1:1:1) transfusion protocol vs laboratory-results-guided transfusion in 78 patients with severe trauma (Nascimento et al. 2013). They concluded that the 1:1:1 protocol could be exposing patients not only to unnecessary blood transfusion but also to increased risk of acute respiratory distress syndrome, sepsis and multiple organ dysfunction.

The *Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study* compared the effectiveness of early transfusion of plasma and/or platelets to time-varying plasma:RBC and platelet:RBC ratios, with the primary outcome of in-hospital mortality. Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received at least three units of blood products over the first

24 hours after admission. In patients who survived 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios, however (Holcomb et al. 2013).

The *Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)* trial compared transfusion of plasma, platelets and red blood cells in a 1:1:1 vs 1:1:2 ratio and found no difference in mortality at 24 hours or at 30 days (Holcomb et al. 2015). More patients in the 1:1:1 group achieved haemostasis and fewer experienced death due to exsanguination by 24 hours.

Formula-driven protocols are not effective to reverse coagulopathy, and result in high complications. FFP transfusion increases the risk of hospital-acquired infection by three (Sarani et al. 2008). Dara and colleagues (2005) found no difference in new bleeding episodes, but new-onset acute lung injury was more frequent in the transfused group (18% vs 4%, p = 0.21). The more plasma used, the more complications. Watson and colleagues (2009) showed that each unit of FFP transfused was associated with a 2.1% higher risk of multi-organ failure (MOF) and 2.5% higher risk of ARDS.

Massive transfusion protocols: plasma first followed by factor concentrates

The alternative to 1:1:1 transfusion is to give plasma first in hypovolaemic situations and then on top factor concentrates. Innerhofer and colleagues investigated exclusive use of CFCs in 144 trauma patients with similar ISS (37-38). One group received coagulation factor (CF) only and the other group was treated with CF+FFP in the emergency room (ER). The primary outcome was the response profile for coagulation parameters and secondary transfusion rates and outcome. **Table 1** shows the transfusion requirements in the first 24 hours. **Table 2** shows the outcomes.

Outcome was worse in the group that received FFP additionally, and there was more ARDS, more MOF, more sepsis, and by day 30 increased mortality. The use of CF alone effectively corrected coagulopathy in patients with severe blunt trauma.

In the RETIC single-centre open label parallel-group crossover study (Innerhofer et al. 2017), patients who were coagulopathic in the ER were randomised to receive FFP or CFC and were monitored for incidence of MOF. Patients who received initially coagulation factors had 50% less massive transfusions. Bleeding was increased in coagulation factor-treated patients, especially those patients who received some kind of rescue therapy. The group treated with plasma and then with coagulation factor had a higher MOF score.

Therefore a 1:1:1 transfusion protocol is ineffective, but FFP initially and then coagulation factor concentrates also result in higher mortality and higher numbers of massively transfused patients.

Goal-directed treatment of trauma-induced coagulopathy

Gonzalez and colleagues (2016) found that using a goal-directed, thromboelastography-guided massive transfusion protocol (MTP) to resuscitate severely injured patients improved survival and used less plasma and platelet transfusions during the early phase of resuscitation, compared with an MTP guided by conventional coagulation assays. Kaserer and colleagues (2018) compared two different coagulation algorithms (a target haematocrit range vs a lower haematocrit limit only and goal-directed coagulation algorithm vs blind coagulation package) and effect on use of allogenic blood products and coagulation factors in a retrospective multicentre observational study of severely injured trauma patients (Kaserer et al. 2018). Factor XIII substitution was considered early. They found that a goal-directed coagulation algorithm led to

Table 1. Transfusion and coagulation factor requirements during the first 24 h in trauma patients treated with CF or CF+FFP

	CF n=66	CF + FFP n=78	p value
RBC (U)	2 (0, 4)	9 (5, 12)	< 0.001
FFP (U)	0 (0, 0)	10 (5, 13)	< 0.009
PC (U)	0 (0, 0)	1 (0, 2)	< 0.001
Fibrinogen concentrate (g) Patients treated (n)	4 (2, 4) 66 (100)	4 (2, 7) 70 (89.7)	0.0007 0.1252
PCC (IE) Patients treated (n)	0 (0, 1000) 23 (34.8)	750 (0, 1800) 40 (51.3)	0.0006 0.064

RBC red blood cell concentrate FFP fresh frozen plasma PC aphaeresis platelet concentrate PCC prothrombin complex concentrate (factors II, VII; IX, X) NT not tested.
Source: Innerhofer et al. 2013

Table 2. Outcome parameters of the full unmatched trauma population

	CF Group (*n* = 66)	FFP Group (*n* = 78)	*p*-Value
paO_2/FiO_2 24 h	317 (250, 377)	241 (201, 325)	0.002
Ventilator-free days	18 (8, 25)	16 (4, 23)	0.139
Sepsis (*n*)	11 (16.9)	28 (35.9)	0.014
MOF (*n*)	12 (18.2)	29 (37.2)	0.015
ICU stay (days)	12 (6, 24)	14 (7, 30)	0.217
LOS (days)	24 (12, 35)	29 (16, 50)	0.074
30-day mortality (*n*)	5 (7.6)	6 (7.7)	0.979
Thromboembolism (*n*)	6 (10.0)	6 (7.7)	0.772

Data are given as median (interquartile range) or numbers (%).
ICU intensive care unit LOS length of hospital stay MOF multi-organ failure
Source: Innerhofer et al. 2013

Figure 1

Source: Fries et al. 2017

less transfusion of RBC.

Stein and colleagues evaluated the results of changing the transfusion algorithm from 2007 when they introduced a coagulation trauma algorithm. They reduced ventilator days, mortality, FFP and RBC transfusion (Stein et al. 2017).

Figure 1 summarises the evidence for goal-directed therapy's effect on 28- or 30-day mortality.

The white spheres are larger as the number of patients included was larger, and mortality was higher (Fries et al. 2017). ■

Abbreviations

ARDS acute respiratory distress syndrome
ER emergency room
FFP fresh frozen plasma
ISS injury severity score
MOF multi-organ failure
PRBC packed red blood cells
PT prothrombin time
RBC red blood cells

Conclusion/ Key points

- Trauma is never standardised, patients are never standardised so a standard regime is not possible
- Do not start with massive transfusion algorithms for bleeding trauma patients
- Goal-directed therapy of coagulopathy is recommended for trauma patients

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Xenon limits brain damage following cardiac arrest

Xenon and brain injury

Xenon, a chemically inert but biologically active monatomic gas, has been applied in patients for anaesthesia/sedation, and most recently in the critical care of patients with acute ongoing neurological damage.

Following preclinical evidence that xenon has ameliorative activity in several pathobiologic pathways that are involved in central nervous system injury, xenon was shown to be effective at improving both morphology and function in a series of models of hypoxic/ischaemic injury that simulate stroke (both haemorrhagic and ischaemic), neonatal asphyxia, as well as the ischaemic-reperfusion injury that occurs in the post-cardiac arrest syndrome (PCAS).

These promising findings prompted a Phase 2 RCT that revealed that a 24-hour xenon administration during targeted temperature management (TTM) resulted in significantly less brain damage than TTM alone in PCAS. A pivotal, multicentre, Phase 3 RCT is now underway to establish the efficacy (primary endpoint is survival with good functional outcome) and safety of xenon in PCAS.

Anaesthetic and sedative agents are typically administered in perioperative settings to facilitate surgical and discomfort-inducing procedures. Because of the pleiotropic effects of these powerful drugs, investigators have trialled these agents for other indications including the use of ketamine for refractory depression (McCloud et al. 2015), dexmedetomidine to facilitate detoxification from alcohol and substance abuse disorders (Wong et al. 2015), and propofol for nausea and vomiting (Griffiths et al. 2012).

Following the market authorisation for general anaesthesia in 2007, xenon's use has extended to organ protection because of its multifaceted cytoprotective actions (Maze 2016). In this report, we focus on the neuroprotective properties of xenon.

Neuroprotective targets in acute ongoing neurologic injury

Prior to considering the possible clinical applications of xenon, we reflect on the pathophysiologic processes that characterise the clinical conditions for which xenon's neuroprotective properties may be exploited.

Similar, but not identical, pathophysiologic mechanisms propagate ongoing damage whether the acute neurological injury is initiated by a stroke (i.e. ischaemic and haemorrhagic), cardiac arrest, or traumatic brain injury.

Stroke

Ischaemia is the cause in ~85% of adult stroke victims. Dirnagl and colleagues (2014; 1999) have offered important insights into the potentially-modifiable processes that obtain in ischaemic stroke (**Figure 1**). Sudden interruption of perfusion to discrete brain regions heralds a phase of excitotoxicity due to ischaemia-induced depolarisation of glutamatergic neurons causing release of the excitatory neurotransmitter, glutamate. Activation by glutamate of its cognate receptor subtypes results in a massive influx of calcium cations that produces neuronal death through necrosis. In the subacute phase of ischaemic stroke, cell death occurs through apoptotic processes. In the later phases brain damage can be produced by inflammatory processes initiated by engagement of the innate immune response (Dirnagl et al. 1999).

The haemorrhagic form of stroke is mainly caused by subarachnoid and intracerebral haemorrhage. The former type accounts for 5 % to 10% of all strokes and is mostly attributed to rupture of an aneurysm. Apart from the decreased perfusion and ischaemia in the territory of the ruptured blood vessel engendering excitotoxicity, additional pathophysiologic processes supervene due to the collection of extravascular blood (cytotoxic effect) (Budohoski et al. 2014). Because of perturbed cerebrospinal fluid hydrodynamics, the intracranial pressure may rise resulting in failure to adequately perfuse other brain regions. Together with vasospasm, disruption of the blood-brain barrier and the supervention of inflammation, delayed cerebral ischaemia exacerbates the patient's neurologic deficits. However, the contribution of vasospasm to delayed cerebral injury following subarachnoid haemorrhage (SAH) has been challenged (Budohoski et al. 2014). It is notable that SAH remains an unmet treatment challenge,

and novel interventions, including xenon, are worthy of consideration.

Cardiac arrest

Cardiac arrest is the classical example of ischaemic-reperfusion injury in which the absence of any perfusion to the brain provokes excitotoxicity (Neumar et al. 2008). Successful resuscitation and restoration of spontaneous circulation causes a new pathophysiologic process characterised by apoptosis and neuroinflammation.

Traumatic brain injury

Traumatic brain injury encompasses heterogeneous conditions from diverse types of trauma of varying severity; as such, different pathophysiological pathways may be involved and major international efforts are more precisely characterising the evolution of injury (International Initiative for Traumatic Brain Injury Research [InTBIR - **intbir.nih.gov**]; Transforming Research and Clinical Knowledge in Traumatic Brain Injury [TRACKTBI - **tracktbi.ucsf.edu**]). From these efforts, much has been learned about genetic factors that modulate the host-response to injury by proteins such as apolipoprotein E 4 (Lawrence et al. 2015), mitochondrial DNA haplotype (Bulstrode et al. 2014) and brain-derived neurotrophic factor (Failla et al. 2016). Physiologic monitoring has yielded information on dysregulation of intracranial pressure, autoregulation of brain perfusion, brain oxygenation and metabolism, inflammation and cortical electrical activity. Macroscopically several types of lesions can be distinguished including shearing of white matter tracts, contusions, haematomas and oedema. A secondary wave of damage occurs hours to days after the traumatic event that is characterised by excitotoxicty, free radical generation, mitochondrial dysfunction, mass effect, ischaemia and inflammatory responses (Maas et al. 2008). Especially in the setting of repetitive trauma, processes are initiated that result in long-term consequences such as dementia, Parkinsonism, and epilepsy.

Neuroprotective properties of xenon

Xenon is an antagonist of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor (Franks et al. 1998), a pivotal mediator of the excitotoxicity that is ubiquitously present in acute ongoing neurological injury from a variety of causes. NMDA-receptor antagonists are neuroprotective in in vitro and in vivo brain injury models (Choi et al. 1988). Interventions, such as ketamine, that produce NMDA antagonism through ion pore blockade, result in the development of "Olney's lesions" with psychotomimetic effects (Olney et al. 1991). Xenon produces its NMDA antagonism by competing with glycine at the co-activation site (Dickinson et al. 2007); hence xenon does not induce the Olney's lesions or behavioural changes that characterise the direct ion pore blockers. In fact, xenon ameliorates the injury produced by other NMDA-receptor antagonists (Nagata et al. 2001). Xenon protects against injury induced by NMDA, glutamate or oxygen-glucose deprivation (Wilhelm et al. 2002). Other complementary neuroprotective properties of xenon include interruption of apoptosis (Ma et al. 2005), activation of species of ion channels that result in membrane hyperpolarisation (Bantel et al. 2010; Gruss et al. 2004) and a generalised cytoprotective action initiated by upregulation of hypoxia-inducible factor-1α (HIF-1α) and its downstream protective effectors (namely, erythropoietin) within the brain under normoxic conditions (Ma et al. 2009).

The neuroprotective properties of xenon have been corroborated in preclinical models of hypoxic ischemic encephalopathy (Wilhelm et al. 2002; Ma et al. 2006; Dingley 2006; Rajakumaraswamy et al. 2006; Dingley et al. 2008; Cattano et al. 2008; Valleggi et al. 2008; Luo et al. 2008; Bantel et al. 2009,) stroke (Homi et al. 2003; David et al. 2003; Limatola et al. 2010; David et al. 2010; Sheng et al. 2012), traumatic brain injury (Coburn et al. 2008; Harris et al. 2013; Campos-Pires et al. 2015,Campos-Pires et al. 2018) anaesthetic-induced developmental neurotoxicity (Ma et al. 2007; Cattano et al. 2008a; Shu et al. 2010; Cattano et al. 2011; Sabir et al. 2013), and cardiac arrest (Schmidt et al. 2005; Fries et al. 2008; Fries et al. 2012). Preclinical studies have also shown that xenon and targeted temperature management (TTM; currently, the standard of care for post-cardiac arrest syndrome) can be combined to protect in an additive or super-additive (synergistic) manner. Data, published in eight peer-reviewed manuscripts from four different laboratories involving four preclinical injury models, demonstrate that xenon's neuroprotective action is most

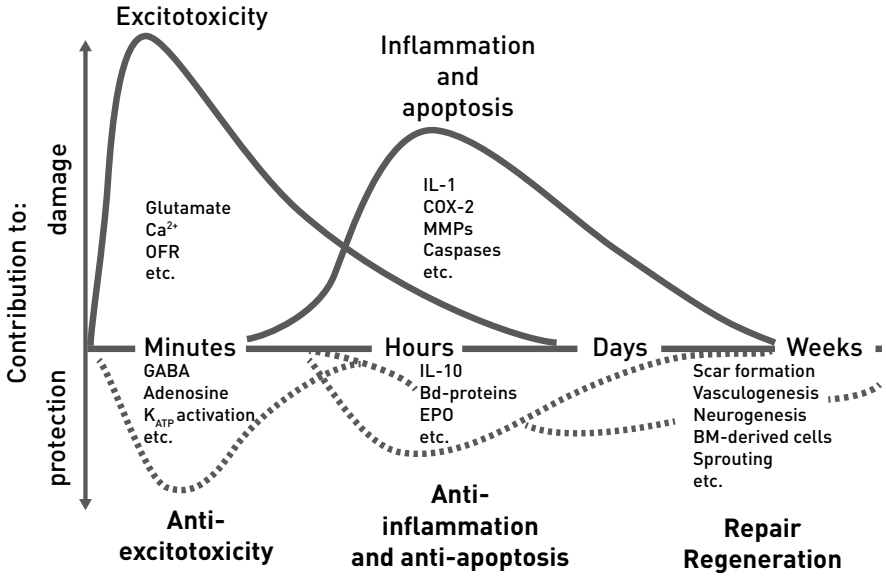

Figure 1. Pathobiologic changes following ischaemic stroke

In this schematic diagram the major damage-inducing changes following ischaemic stroke are depicted over time following the acute ictus. Also depicted are the mechanisms that can protect against the damage at the various epochs during stroke evolution (Modified from Dirnagl et al. 2014). Reproduced with permission.

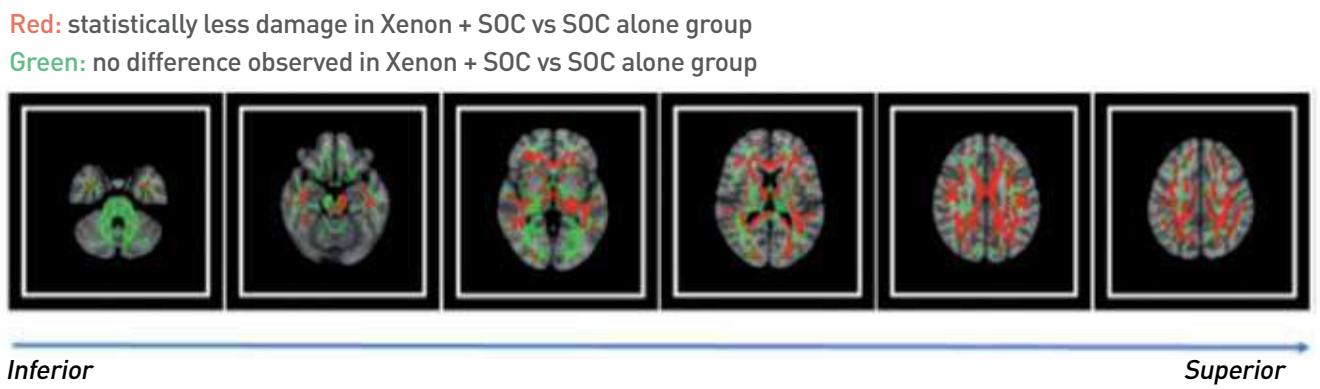

Figure 2. Differences in white matter tract injury between standard of care (SOC) vs Xenon + SOC groups in patients with post-cardiac arrest syndrome

Saggital plane sections of the overlaid white matter tracts (inferior to superior) are illustrated in which red indicates tracts with statistically less damage (higher fractional anisotropy) in the xenon + SOC group vs. SOC alone group. In green are tracts that are no different between the two groups either because no injury occurred or because xenon did not reverse injury in these tracts. In no tracts was injury significantly less severe in the control group. (Modified from Laitio et al. 2016). Reproduced with permission.

effective when body temperature is reduced (Ma et al. 2005; Martin et al. 2007; Hobbs et al. 2008; Thoresen et al. 2009; Chakkarapani et al. 2010; Faulkner et al. 2011; Fries et al. 2012; Sabir et al. 2014). Unlike other neuroprotective strategies, including a different NMDA-receptor antagonist (gavestinel), xenon alone exhibits this enhanced efficacy when temperature is reduced.

Clinical evidence for the neuroprotective properties of xenon

The Xe-hypotheca trial (NCT 00879892 - clinicaltrials.gov/ct2/show/NCT00879892) studied the Effect of Inhaled Xenon on Cerebral White Matter Damage in Comatose Survivors following an Out-of-Hospital Cardiac Arrest (Laitio et al. 2016). The trial, which was undertaken at the medical centres of Turku and Helsinki Universities in Finland, enrolled 110 successfully resuscitated (restoration of spontaneous circulation [ROSC] within 45 minutes of a witnessed cardiac arrest with an initial shockable rhythm) but still comatose patients. The trial compared xenon (up to 50% by inhalation) plus the standard of care (SOC) versus SOC alone for the primary endpoint of white matter brain damage (global fractional anisotropy [GFA] derived from a diffusion tensor imaging sequence); both arms were inclusive of TTM administered for 24 hrs. Assessment of the GFA revealed significantly (P=0.006) reduced brain damage in the subjects randomised to receive xenon. There was 41.7% less damage to white matter tracts (from the approximately 115,000 voxels assessed in each patient) in the Xenon + SOC vs SOC. alone group. The relative damage to the major white matter tracts in the two groups is depicted (**Figure 2**).

> **"subarachnoid haemorrhage remains an unmet treatment challenge and novel interventions, including xenon, are worthy of consideration"**

Xe-HYPOTHECA was not powered to detect differences in functional endpoints; reduction in 6-month mortality rate - 27% in the xenon group and 35% in the SOC group (adjusted hazard ratio, 0.49 [95% CI, 0.23-1.01]) - did not achieve statistical significance (P = 0.053). The degree of white matter injury was the strongest predictor of mortality at 6 months.

Clinical evidence for the myocardial protective properties of xenon

A predefined secondary objective of the XeHypotheCA Trial was to assess the effect of inhaled xenon on myocardial ischaemic damage. Troponin-T (TnT) levels were measured at hospital admission, and at 24h, 48h and 72h post-cardiac arrest (Arola et al. 2017). The baseline characteristics did not differ significantly between the groups. Results are tabulated (**Table 1**). After adjustments for age, gender, study site, primary coronary percutaneous intervention (PCI), and norepinephrine dose, the mean standard deviation post-arrival incremental change of the ln-transformed troponin-T at 72 hours was 0.79 (1.54) in the xenon group and 1.56 (1.38) in the control group (adjusted mean difference, -0.66 [95% CI, -1.16 — -0.16], P=0.01). The decline of TnT from the peak value at 24h to 72h was significantly greater in the xenon group than in the control group (p =0.0008). The effect of xenon on the change in the troponin-T values did not differ in patients with or without PCI or in those with a diagnosis of ST-elevation myocardial infarction (group by PCI or STEMI interaction effect, P=0.86 and P=0.71, respectively). In comparison with hypothermia alone, inhaled xenon combined with hypothermia resulted in less severe myocardial injury as demonstrated by the significantly reduced release of troponin-T.

Future applications of xenon for critical care

Apart from the potential use of xenon for postoperative sedation (Bedi et al. 2003), and for selected intraoperative settings, e.g., for neurosurgical procedures (Rylova and Maze 2018) it is unlikely that xenon will be considered for routine use in perioperative settings both because of the availability of cheaper alternatives and because of the

Table 1. Troponin-T change from baseline to 72 h after OHCA

	Xenon Group (n = 54)	Control Group (n = 54)	Mean Difference (95% CI)		p Value	
			Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Absolute values, µg/l						
Baseline (hospital admission)	0.09 (0.03-0.30)	0.08 (0.04-0.23)	–	–	–	–
24 h after OHCA	0.38 (0.15-1.27)	0.47 (0.12-1.74)	–	–	–	–
48 h after OHCA	0.25 (0.09-0.85)	0.41 (0.10-1.48)	–	–	–	–
72 h after OHCA	0.22 (0.05-0.69)[b]	0.40 (0.14-1.87)[c]	–	–	–	–
ln-transformed change from baseline						
ln ΔTnT 24 h	1.40 ± 1.39	1.65 ± 1.38	−0.26 (-0.79 to 0.27)	−0.16 (−0.62 to 0.30)	0.33	0.49
ln ΔTnT 48 h	1.00 ± 1.37	1.28 ± 1.38	−0.28 (-0.80 to 0.25)	−0.18 (−0.63 to 0.27)	0.29	0.43
ln ΔTnT 72 h	0.79 ± 1.54[b]	1.56 ± 1.38[c]	−0.76 (−1.33 to −0.20)	−0.66 (−1.16 to −0.16)	0.009	0.01

Source: Adapted from Arola et al. 2017, Table 3.
Δ change from the baseline CI confidence interval ln natural logarithm OHCA out-of-hospital cardiac arrest TnT troponin-T
Note 1: Values are median (interquartile range) or mean ± standard deviation, unless otherwise indicated.
Note 2: Natural logarithmic transformation for troponin-T values was used in the statistical analysis due to skewness of the data.
a Data are adjusted for age, sex, study site, percutaneous coronary intervention, and dose of noradrenalin during the first 24 h after intensive care admission.
b Data are for 52 patients due to missing data of 2 patients at 72 h.
c Data are for 53 patients due to missing data of 1 patient at 72 h.

need for recirculating systems to minimise consumption of xenon.

Nonetheless, in critical care settings where there is an unmet medical need, e.g., Post-Cardiac Arrest Syndrome, xenon's cytoprotective effects may be further appreciated for its physico-chemical properties that result in a near instantaneous onset of action together with a low potential for toxicity through its chemical non-reactivity. A pivotal 1436-patient Phase 3 Trial (Xenon for Neuroprotection During Post-Cardiac Arrest Syndrome in Comatose Survivors of an Out of Hospital Cardiac Arrest (XePOHCAS - NCT03176186 - **clinicaltrials.gov/ct2/show/NCT03176186**]) has been launched to determine the efficacy and safety of 24h inhalation of xenon to improve survival with good functional outcome in successfully resuscitated (ROSC ≤ 30 min), but still comatose, victims of a witnessed cardiac arrest.

Production and availability of xenon

Xenon is an extremely rare element present in the atmosphere at approximately 88 parts/billion. Xenon is produced by a process of cryogenic distillation in which air is fractionated into its primary components by cooling at high pressure until it liquefies; the different components are then separated according to physical characteristics, including boiling points and density, within specialised cryogenic columns. The process consumes large amounts of energy and those fractions which are found in low concentrations (i.e., xenon) require multiple distillations, and are therefore extremely expensive to produce to medical grade purity of 99.999%. The estimated total supply of xenon is thought to be 14 million litres, of which 50% could theoretically be delivered in medical grade. Approximately 50L of xenon is required for a 24-hour intervention; under these conditions approximately 140,000 patients could be treated annually.

Conclusions

Xenon, the noble elemental gas, may benefit the critically ill patient that has ongoing acute neurological injury because it reduces the activity in several of the pathobiologic pathways that obtain in these conditions. A definitive, pivotal, multicentre, trial to establish xenon's safety and efficacy in the setting of post-cardiac arrest syndrome is now being prosecuted. If successful, the next challenge will be to increase the production of medical grade xenon through the retrofitting of oxygen-purification plants. Further refinements in the recirculation and recycling of xenon can further improve the availability of this scarce resource.

Conflict of interest

Mervyn Maze is a co-founder, and shareholder of equity in NPXe Ltd, a company that seeks to commercialise neuroprotective applications of xenon. TL is a member of the Trial Executive Committee for XePOHCAS, a phase 3 RCT designed to test the efficacy and safety of patients with post-cardiac arrest syndrome. The XePOHCAS trial is sponsored by NeuroproteXeon. ■

Abbreviations

PCAS post-cardiac arrest syndrome
ROSC return of spontaneous circulation
SOC standard of care
TnT Troponin-T
TTM targeted temperature management

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What's new in sepsis in children?

The latest in diagnosis and treatment

Sepsis is a life-threatening condition in children. Current paediatric definitions are based on systemic inflammatory response syndrome. Since the publication of the third international consensus definitions for sepsis and septic shock for adults, efforts in paediatrics are focused on finding a definition that involves a premature diagnosis with prognostic implications based on the organic dysfunction as in the adult patient. The latest clinical guidelines on haemodynamic support are by the American College of Critical Care Medicine. Initial resuscitation and fluid response is guided by minimal invasive monitoring. In PICU monitoring should be intensified and goals should be appropriate perfusion pressure $ScvO_2$ ≥70% and CI ≥3.3 ≤ 6.0 L/min/m^2. In fluid-resistant shock adrenaline is the initial inotrope (peripheral infusion is possible), except in consistent warm shock when noradrenaline may be the first drug. Then the shock pattern will determine the additional drugs.

Sepsis is a life-threatening condition in children. The lack of a clear definition leads to a heterogeneous diagnosis that prevents obtaining fully reliable epidemiological data. In the study conducted by Weiss et al. (2015) the Paediatric Intensive Care Unit (PICU) prevalence worldwide was 8.2% (Europe 6.2%), and mortality was 25%, and did not differ by age or between developed and resource-limited countries. For community-acquired sepsis in European PICUs, mortality was 6%, increasing to 10% in the presence of septic shock. Of the survivors, 31% were discharged with disability (Boeddha et al. 2018).

In 2005, the Barcelona Consensus Conference constituted by paediatric experts published the paediatric definitions, which were based on systemic inflammatory response syndrome (SIRS) criteria (Goldstein et al. 2005), approaching the adult definitions of 1991 and 2001. To date, these criteria have been the most widely used to define and classify septic patients in children.

Use of the SIRS criteria has been criticised in recent years because of their non-specificity. On the other hand, there are patients who may not have two or more SIRS criteria and suffer an infection with organ failure (Weiss et al. 2015; Brown et al 2015).

The third international consensus definitions for sepsis for adults (Sepsis-3) (Singer et al. 2016) agreed on new criteria based on organ dysfunction. Sepsis is now defined as the organ dysfunction that appears due to the inflammatory host response to an infection (10% death risk). The Sepsis-3 definitions aim to simplify the diagnosis and allow premature detection of patients with organ failure, at a higher risk of death. Organ dysfunction is measured as an acute increase of two points in the Sequential Organ Failure Assessment Scale (SOFA) due to an infection. Blood tests are necessary to define SOFA, so it can be a non-optimal tool outside the ICU. For this reason the use of quick SOFA (qSOFA) has been proposed.

As far as the paediatric patient is concerned, what influence can the Sepsis-3 definitions have? A consensus has not been published since 2005, and the latest paediatric Surviving Sepsis Campaign (SSC) guidelines have not yet been published; the last update was published in 2013. Presumably, the inclusion of the concept of organ dysfunction in the definition of sepsis will be shared by the community of paediatricians. Efforts are focused on finding a definition that involves a premature diagnosis with prognostic implications based on the organ dysfunction as well as in the adult patient. The SOFA score has not been designed for use in children, a population that has different vital signs according to age. At present, attempts are being made to adapt the definitions established for adults through a paediatric score.

The use of Sepsis-3 definitions in children was feasible and showed promising results. Schlapbach and colleagues (2017) demonstrated that the two SIRS variables-based sepsis criteria had poor specificity to discriminate children with infection at substantially higher mortality risk. Moreover, age-adapted SOFA and Paediatric Logistic Organ Dysfunction-2 score (PELOD-2) had significantly greater prognostic accuracy for in-hospital mortal-

ity. Their findings indicate that age-specific translation of Sepsis-3 definitions to critically ill children using validated measures of organ dysfunction should be considered in the next revision of paediatric sepsis definitions. In contrast, the performance of qSOFA to identify patients with organ dysfunction at risk for worse outcomes was poor, and may not be of sufficient clinical value to be recommended as a screening tool for paediatric age groups within the ICU. Leclerc and colleagues (2017) concluded that in children admitted to PICU with suspected infection, PELOD-2 score on day 1 was highly predictive of PICU mortality, suggesting its use to standardise definitions and diagnostic criteria of paediatric sepsis. The SOFA score was adapted and validated with age-adjusted cutoffs in critically ill children: paediatric SOFA (pSOFA). Sepsis-3 definitions were assessed in children with confirmed or suspected infection (Matics et al. 2017). All these scores might be more useful for prognosis than for diagnosis of sepsis.

Regarding biomarkers, values of C-reactive protein and procalcitonin have been included in the usual management although their sensitivity and specificity is lower than desired. Lactate continues to be valid because its elevation is related to organ dysfunction and worse prognosis; monitoring its levels can also assess the therapeutic response. New hopes are focused on other biological markers, such as adrenomoduline (Jordan et al. 2014) or pro-inflammatory and anti-inflammatory cytokines (Polic et al. 2017), to help us in diagnosis, prognosis, and follow-up. We do not have a perfect biomarker to date; perhaps in the future a panel of different biomarkers may be the key (Lamping et al. 2018).

Treatment

The latest SSC guidelines that include paediatric management date from 2012 (Dellinger et al. 2013). The American College of Critical Care Medicine (ACCM) published in 2017 the guide for haemodynamic support in neonates and children with septic shock (Davis et al. 2017).

Despite the dissemination of the previous guidelines, some studies demonstrated incomplete adherence to recommendations (Moresco et al. 2018). Consequently quality improvement studies were designed, in order to trigger rapid clinician evaluation and implementation of appropriate resuscitation efforts (Esteban et al. 2017; Cruz et al 2011). The new ACCM guidelines recommend that each institution implements its own adopted or home-grown bundles resuscitation and stabilisation bundle to drive adherence to consensus best practice.

The first hour of resuscitation

The goals of the first hour should be to maintain the airway, oxygenation, and ventilation; Maintain or restore circulation, capillary refill, normal pulses, urine output ≥ 1 mL/kg/hr, normal mental status, normal blood pressure for age; and restore appropriate heart rate (HR).

> **"new studies in children to diagnose and classify sepsis according to organ failure-based scores are promising"**

During initial resuscitation the achievement of objectives is evaluated by minimal invasive monitoring. Echocardiography is considered an appropriate noninvasive tool to evaluate myocardial contractility and intravascular volume, to direct resuscitation goals and therapeutic endpoints.

Supplemental high-flow oxygen should be provided. Children with persistent or worsening shock should be intubated and receive mechanical ventilation to eliminate breathing effort and improve oxygenation and organ perfusion. In most cases, there is time for fluid resuscitation and starting a peripheral inotropic infusion before airway management is needed. Patients with these characteristics are vulnerable to the haemodynamic effects of sedatives (Li et al. 2016), emphasising the importance of initial resuscitation prior to airway instrumentation. The use of ketamine with atropine is considered to be the induction regimen which best promotes cardiovascular integrity. The use of etomidate is discouraged given its effects on adrenal function. Other options to consider are fentanyl and remifentanil or benzodiazepines titrated with small doses. Barbiturates, inhalational agents or propofol are not appropriate. Neuromuscular blocking agents may facilitate intubation.

Vascular access should be rapidly accomplished. Portable near-infrared imaging devices may assist in peripheral vascular access. Establish intraosseous access if peripheral intravenous line access cannot be attained in 5-10 minutes. Establishing a central venous catheter during the initial resuscitation should not delay or compromise the resuscitation efforts. Ultrasound guidance may facilitate placement of central catheters.

Extract sample for blood analysis and culture when a vascular access is accomplished. Initiate antibiotic therapy as soon as possible after obtaining cultures and always during the first hour of clinical suspicion.

Fluid resuscitation should start immediately unless hepatomegaly, rales, or a cardiac gallop are present. If these signs are present, the patient may not require fluid boluses and instead, inotropic support is recommended. The harm of fluid boluses at the initial haemodynamic resuscitation is a concern (Frazier et al. 2015). Fluid infusion (crystalloids or colloids) is best initiated with boluses of 20 mL/kg, titrated to assuring signs of restored circulation and normal HR as commented above. Initial (first hour) volume resuscitation requirements commonly are 40–60 mL/kg. Specific evaluation after each bolus for signs of fluid overload and simple algorithms are needed to support healthcare providers to choose which patients could be harmed and which will benefit from fluid boluses (Ford et al. 2012; Parker et al. 2016).

Patients who do not respond rapidly to initial fluid boluses should be considered for invasive haemodynamic monitoring. In the fluid refractory patient, begin a peripheral epinephrine, while establishing a central venous catheter. Dopamine, epinephrine, or norepinephrine can be administered as a first-line drug as indicated by haemodynamic state when a central line is available.

Beyond the first hour (PICU haemodynamic support)

Monitoring should be intensified by adding invasive instruments to the clinical objectives: central venous access, arterial pressure

monitoring and a modality to assess cardiac output (CO) are recommended.

Goal-directed therapy to achieve:

1. Perfusion pressure (mean arterial pressure (MAP)-central venous pressure (CVP) or MAP- intra-abdominal pressure (IAP)) appropriate for age. It is considered necessary for organ perfusion.
2. Venous oxygen saturation ($ScvO_2$) greater than 70% is associated with improved outcome. $ScvO_2$ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand.
3. Cardiac index (CI) greater than 3.3 and less than 6.0 L/min/m^2 may result in improved survival. Contrary to the adult experience, low CO, not low systemic vascular resistance (SVR), is associated with mortality in paediatric septic shock.

Normal INR, anion gap, and lactate are also objectives at this point.

Fluid losses and persistent hypovolaemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be monitored carefully to evaluate bolus response. Crystalloid is the fluid of choice in patients with haemoglobin greater than 10 g/dL. Red blood cells transfusion can be given to children with haemoglobin less than 10 g/dL. Fresh frozen plasma is recommended for patients with prolonged INR (infusion, not bolus). Following shock resuscitation, diuretics/peritoneal dialysis/high flux continuous renal replacement therapy can be used to remove fluid in patients who are fluid overloaded and unable to maintain fluid balance.

Septic shock represents a dynamic process so haemodynamic drugs selected and their infusion dose may need to be changed over time. Frequent re-evaluation of haemodynamic parameters is recommended as haemodynamic support can be required for days.

For children with "fluid-resistant shock" adrenaline is the initial inotrope (dopamine loses prominence), except in a clear pattern of low resistance and hypotension when noradrenaline may be the first drug. Catecholamine-resistant shock can present with low CO/high SVR, high CO/low SVR, or low CO/low SVR shock (**Table 1**), which will determine following treatment.

Table 1. Haemodynamic support algorithm, based on American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Paediatric and Neonatal Septic Shock. Crit Care Med. 2017;45:1061-93.

Low CI, Normal BP, High SVR	Low CI, Low BP, Low SVR	High CI, low BP, Low SVR
Epinephrine, mid dosage dopamine or dobutamine (tends to lower SVR)	Epinephrine	Dopamine, epinephrine or norepinephrine
1. Milrinone (to recruit microcirculation) 2. Nitroprusside or nitroglycerin (second-line vasodilators) 3. Levosimendan/enoximone (if no response to previous) Discontinue if arrhythmia or hypotension	1. Norepinephrine (to increase diastolic blood pressure and SVR) 2. Dobutamine, milrinone, enoximone, levosimendan (once adequate blood pressure is achieved, to improve CI and SvO_2)	1. Titrate norepinephrine and fluid (if consistent warm shock) 2. Low-dose vasopresine, angiotensin or terlipresin (to restore BP) 3. Invasodilator (excessive vasoconstriction compromise microcirculation, can reduce CO and distal necrosis can occur)

BP blood pressure CI cardiac index CO cardiac output SVR systemic vascular resistance

Angiotensin II has been recently reported as an effective treatment in patients with refractory vasodilatory shock (Khanna et al. 2017). Due to the lack of specific paediatric trials, its use in children remains prudent despite exceptional experiences (Yunge et al. 2000).

Consider hydrocortisone in refractory shock in children at risk of adrenal insufficiency. Extracorporeal membrane oxygenation (ECMO) is a viable therapy for refractory septic shock in neonates and children (Solé et al. 2018). Paediatric and adult patients with sepsis have lower survival (historically ≤ 50%) than neonates (80% + survival), but experienced ECMO centres are now reporting survival rates approaching 75% (MacLaren et al. 2011).

Outcome benefits of CRRT (management of fluid overload, acute kidney injury, clearance of lactate or inflammatory, etc.), either alone or in tandem with ECMO, should be considered in paediatric sepsis.

Regarding blood purification, in 2010 the American Society of Apheresis gave a category III recommendation, which is "Optimum role of apheresis therapy is not established. Decision-making should be individualized". Therapeutic plasma exchange could be considered as a strategy to reverse multi-organ dysfunction syndrome especially in patients with significant coagulopathy.

Conclusion

New studies in children to diagnose and classify sepsis according to organ failure-based scores are promising, and probably a new consensus will approach adult definitions. Adrenaline and noradrenaline will play a major role in shock treatment in children, dopamine being less recommended. We expect the publication of the new paediatric SSC guidelines and new consensus in the following months. ■

Abbreviations

ACCM American College of Critical Care Medicine
BP blood pressure
CI cardiac index
CO cardiac output
CRRT continuous renal replacement therapy
CVP central venous pressure
ECMO extracorporeal membrane oxygenation
HR heart rate
IAP intra-abdominal pressure
ICU intensive care unit
INR international normalised ratio
MAP mean arterial pressure
PELOD-2 Paediatric Logistic Organ Dysfunction-2 score
PICU Paediatric Intensive Care Unit
pSOFA paediatric Sequential Organ Failure Assessment scale
qSOFA quick Sequential Organ Failure Assessment scale
RBC red blood cells
$ScvO_2$ Venous oxygen saturation
SIRS Systemic Inflammatory Response Syndrome
SOFA Sequential Organ Failure Assessment scale
SSC Surviving Sepsis Campaign
SVR systemic vascular resistance

References

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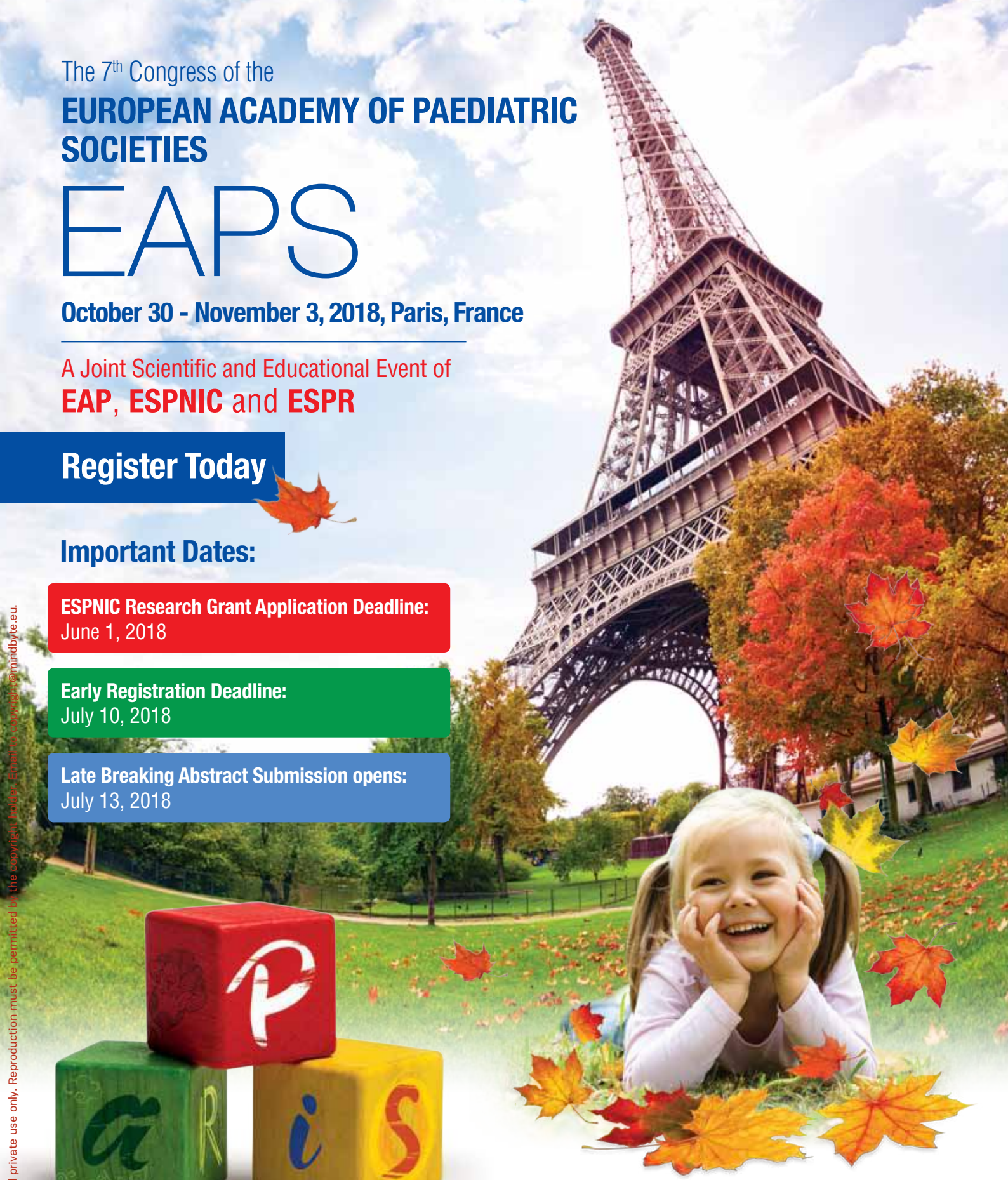

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Optimising sleep in the ICU

Disordered sleep is common in ICU patients. While many of the reasons for this are impossible to modify, and others rely on improvement in the underlying condition, many directly depend on the actions of the treating team: for example, exposure to noise, timing of therapeutic procedures, tapering of sedating drug doses, and daytime mobilisation. Some patients might benefit from nocturnal sedation, but there is reasonable evidence that benzodiazepines and propofol are not the best options. Although unproven in large clinical trials, options including dexmedetomidine, melatonin (and ramelteon), amitriptyline and mirtazapine are all reasonable, especially as their effect is usually able to be assessed over 1-2 nights, facilitating an "n of 1" trial approach to individualised therapy.

Critical illness reduces normal sleep

Most critically ill ICU patients report, recall, or are observed to have disordered sleep. Specifically, the number of awakenings per hour is higher than in health (Elliott et al. 2013; Roche-Campo et al. 2013, Drouot et al. 2014), daytime somnolence is increased to as much as 50% of total sleep (White et al. 1983; Cordoba-Izquierdo et al. 2013), and patients report sleep quality as worse than baseline (Elliott et al. 2013; Freedman et al. 1999; Little et al. 2012). EEG recordings show a higher than normal proportion of light to deep sleep and that sedating drugs are primarily responsible for an "atypical sleep" pattern characterised by disorganised delta waves and the absence of k complexes and sleep spindles [summarised in Devlin et al. (2018)]. There are many possible reasons for disordered sleep, and as the importance of each will vary in different patients (**Figure 1**), so will the optimal approach to management.

Sedation is a poor substitute for sleep

Virtually every ICU clinician has at some stage asked: "My patient didn't sleep, could we give a sedative?" The single most important goal of this paper is to explain why this question is analogous to the request "My patient keeps coughing, could we give a muscle relaxant?" Cough is distressing to patients and staff, but a muscle relaxant is a temporary solution that would make many underlying problems worse, while also causing psychological distress. It is much better to make a diagnosis, address underlying causes, and use symptomatic temporising treatments that do not create adverse effects worse than the problem they are designed to treat.

> "commencing or increasing the rate of a sedative infusion is not a rational strategy to treat insomnia in most ICU patients"

Sleep is a physiological state of cognitive and sensory disengagement from the environment (Kamdar et al. 2012) required in some form by all mammals. Various cardiovascular, respiratory, gastrointestinal and thermoregulatory effects are observed, the importance of which is not fully understood. However, acute sleep deprivation experiments are simple to conduct, revealing perceptual distortions within 24-48 hours, followed by delusions then hallucinations and psychosis (Waters et al. 2018). Physical performance (Kirschen et al. 2018) and immune function (Mullington et al. 2010) are also degraded by inadequate sleep.

Despite their ability to produce the outward appearance of sleep, GABA-ergic sedatives used to facilitate tolerance of an endotracheal tube can have the opposite effect. Benzodiazepines increase N2 (light) but reduce N3 (deep—thought to be the most restorative) sleep (Achermann and Borbely 1987; Borbely et al. 1985), as does propofol (Herregods et al. 1989). Similarly, opioids also reduce N3 and REM sleep (Kamdar et al. 2012). Benzodiazepines in particular have been associated with delirium in the ICU (Pandharipande et al. 2006; 2008), and delirium itself is an independent risk for disordered sleep (Devlin et al. 2018). Therefore, commencing or increasing the rate of a sedative infusion is not a rational strategy to treat insomnia in most ICU patients. Rather, specific treatments such as those listed below should be tried first. The pain, agitation/sedation, delirium, immobility, and sleep (PADIS) guidelines recommend against propofol as a strategy to improve the sleep of critically ill patients, and against benzodiazepines in general (Devlin et al. 2018). Of course, there remain many

Figure 1. Word clouds illustrating the relative importance of combinations of factors that might contribute to disturbed sleep in two different ICU patients. Clearly the correct response to each will be different.

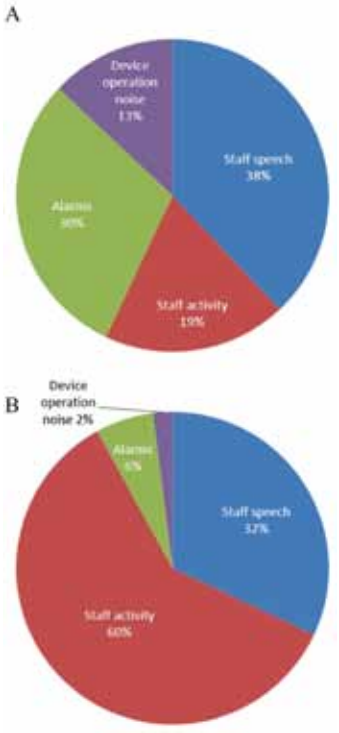

Figure 2. The contribution of each noise category for (A) the acoustic energy and (B) the number of predicted loudness peaks.

specific indications for opioids or GABA-ergic sedatives in the ICU other than sleep.

Measuring sleep

If specific treatments for sleep are to be used, it would be logical to measure their effect using a validated instrument. Regrettably, sleep is more difficult to identify than most other physiological variables, and current tools are so imperfect that recent consensus guidelines (Devlin et al. 2018) recommend against routine clinical use. Nonetheless, technology is advancing rapidly in this area. Polysomnography (electroencephalogram, electromyogram and electrooculogram), the gold standard, is too complex to acquire and interpret for anything but research use. Actigraphy, using motion-sensors on the wrist, while sufficiently accurate in routine sleep studies, over-estimates sleep in critically ill patients who can be immobile for reasons other than sleep (Kamdar et al. 2012). Compressed EEG signals (primarily Bispectral Index, BIS) can estimate sleep depth, but poorly define different stages in sleep architecture and are difficult to use over many hours. Subjective assessment using the Richards-Campbell Sleep Questionnaire (RCSQ) has been validated in ICU patients and correlates well with polysomnography (Richards et al. 2000), and appears better than any technological device at present. An observational study formally comparing all of these measurement approaches is in progress (Delaney et al. 2018).

Non-pharmacological methods to improve sleep

Ventilator mode

The 2018 PADIS guidelines recommended assist-control ventilation over pressure-support ventilation, based on three comparative studies in which sleep had been measured as an outcome (Devlin et al. 2018). All three trials (which together comprised only 61 patients) found a significant benefit in sleep efficiency (proportion of time meant to be asleep actually spent asleep) (18.3% greater, 95% CI 7.9%-28.8%), and also a small but significant increase in the proportion of total sleep time spent in REM sleep. Whether this would also be true for synchronised intermittent mandatory ventilation + pressure support ventilation (SIMV+PSV) (in countries and ICUs where it is the default mode in preference to assist control) was not studied. No recommendation was made on whether adaptive modes of ventilation are beneficial. It is likely that this question is suitable for an "n of 1" trial design—that is, in a patient with insomnia, trial of a night on assist control or SIMV+PSV seems likely to lose little.

Music

One small randomised trial has tested the effect of music on sleep (Su et al. 2013). Participants listened to 45 minutes of classical-type music written specifically for the purpose, or no music. Those played music had significantly lower heart rate, blood pressure, respiratory rate, and spent significantly longer in stage N3 sleep and had significantly better subjective sleep scores.

Reduction of ambient noise

Ambient noise levels in the ICU are approximately double that recommended by the World Health Organization (Darbyshire and

Table 1. Non-pharmacological strategies to improve sleep

Strategy
Ventilator mode (assist-control in preference to pressure support)
Music at sleep time
Reduction of ambient noise
Earplugs
Reduction of ambient light at night
Scheduling of patient care activities during daytime
Tapering of drugs with sedative effects
Daytime mobilisation

Table 2. Drugs to improve sleep

Drug	Suggested dose	Effect on sleep	Known effects on other outcomes
Melatonin	3-10mg	In normal people and people with primary insomnia, reduces time to fall asleep, but no clinically significant effect on time spent asleep. In patients unable to sleep due to a medical cause ("secondary" insomnia), moderate to high quality studies show melatonin has little or no beneficial effect on sleep (Buscemi et al. 2004)	No other benefit has been observed in ICU patients (Devlin et al. 2018)
Ramelteon	8mg	Shortens time to fall asleep and increases total duration of sleep (Neubauer 2008)	Lower incidence and duration of delirium, and fewer night-time awakenings (Nishikimi et al. 2018)
Dexmedetomidine	0.1mcg/kg/hr	Increases total sleep time and proportion of time spent in N2 (deeper) stage of sleep; reduces proportion of time spent in N1 (lighter) sleep. No change in REM sleep (Wu et al. 2016)	Reduced postoperative delirium, reduced reported pain, improved reported sleep (Su et al. 2016)
Amitriptyline	10-50mg	Shortens time to fall asleep and increases overall sleep time, but reduces REM sleep (Wilson and Argyropoulos 2005)	No benefit has been proven in ICU patients when used for this indication
Mirtazapine	15-30mg	Increases total slow wave sleep and REM sleep, as well as improving insomnia scores (Shen et al. 2006)	No benefit has been proven in ICU patients when used for this indication
Trazodone	50mg	Increases total slow wave sleep but reduces REM sleep. Improves subjective insomnia. No effect on total sleep duration or time to fall asleep (Montgomery et al. 1983)	No benefit has been proven in ICU patients when used for this indication

Young, 2013). However, background noise is probably less important for sleep disruption than the frequency and magnitude of peak levels, which were above 85dBA up to 16 times an hour. That this is not the inevitable consequence of electronic devices, mechanical ventilators, etc. was shown by a 2014 Dutch observational study (Simons et al. 2014) that found the loudness peaks (part B of **Figure 2**) were 60% due to staff activity and 32% due to staff speech. Only 6% were due to equipment alarms.

Earplugs

If encouraging clinical staff to be quiet is impossible, another approach could be to use patient earplugs. This is surprisingly effective, as shown by a 2017 meta-analysis of nine studies/1,455 patients (Litton et al. 2016) that found an overall relative risk of delirium of 0.59 (95% CI 0.44-0.78), although not all of the included studies measured sleep. Of those that did, two found earplugs did indeed improve self-reported sleep quality, while one did not observe any significant difference.

Light

Five studies (summarised in Bion et al. 2018) have assessed the effect of reducing environmental light at night. However, each has done this as part of a multi-component intervention that also reduced noise and other disruptions to patient sleep, and all used subjective sleep assessments. The reviewers concluded that this, combined with the different patient populations studied (from non-ventilated neuro ICU patients to mechanically ventilated ICU patients), made it difficult to reach any conclusion about the utility of this intervention alone. Nonetheless, it is difficult to argue against such a low-cost, low risk intervention as turning down the intensity of the lighting at night.

> **"early mobilisation is to date the non-pharmacological intervention associated with the greatest observed reduction in delirium"**

Scheduling of patient care activities

When asked, patients reported that having their vital signs assessed and having blood taken were more disruptive to sleep than any noise (Freedman et al. 1999). Critical care is a 24-hour activity, but whether medication administration, radiographs, wound care, and bathing need to interrupt sleep up to 40-60 times per night (Gabor et al. 2003; Tamburri et al. 2004) really should be questioned. Often these activities are not done for staff convenience but because of the realities of staff rostering; taking this into account at a departmental level might alleviate this major problem.

Tapering of drugs with sedative effects

Many drugs used in critical care have sedating effects, and abrupt withdrawal after a period of habituation leads to a withdrawal state characterised by hyper-alertness and insomnia. Unless there is a good reason, it is usually better to slowly reduce doses of opioids and other sedating medications over several days (Brown et al. 2000) Doing so can avoid the need to simply replace one type of sedative with another.

Mobilisation to restore day-night rhythm

Early mobilisation is to date the non-pharmacological intervention associated with the

greatest observed reduction in delirium (Schweickert et al. 2009). While there are many possible mechanisms for this effect, one must be the likelihood that patients were less likely to be able to sleep during the day, and hence re-established their day-night circadian rhythm earlier than might otherwise have been the case. The cognitive and sleep effects of enhancing other daytime activities are yet to be assessed in critically ill patients.

Drugs to improve sleep

Noting the adverse effects of GABA-ergic drugs when used as sedatives in critical illness, it would seem unwise to choose benzodiazepines as nocturnal sedatives in patients with or recovering from critical illness. While all of the non-pharmacological measures listed above should be considered first, some patients are so distressed by insomnia or so refractory to non-pharmacological treatment that treatment with medication should be at least attempted.

Melatonin

The 2018 PADIS guidelines make no recommendation regarding melatonin and sleep, based on three identified trials they class of low quality that enrolled a total of only 60 patients (Devlin et al. 2018). At least three more trials are planned or already recruiting in ICU populations (*Prevention of Delirium in Intensive Care by Melatonin (DEMEL)* [clinicaltrials.gov/ct2/show/NCT03524937], *Melatonin Use in the Intensive Care Elderly Population (MICE)* [clinicaltrials.gov/ct2/show/NCT03013790], and *Melatonin for Prevention of Delirium in Critically Ill Patients (MELLOW-1)* [clinicaltrials.gov/ct2/show/NCT02615340].

Ramelteon

One small randomised controlled trial of the melatonin-receptor agonist ramelteon was published in 2018, and two larger trials (*Melatonin for Prevention of Delirium in Critically Ill Patients (MELLOW-1)* [clinicaltrials.gov/ct2/show/NCT02615340] and *Pro-phylactic administration of Melatonin for the prevention of Delirium in Intensive Care units* – a randomized placebo controlled trial (Pro-MEDIC study) ACTRN12616000436471 [anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369434] are currently underway. In the published single-centre study of 88 patients, the 45 who received 8mg/d ramelteon had nearly half the incidence of delirium (24.4% vs. 46.5%, p=0.04) of nearly half the duration (0.78 vs 1.40 days, p=0.048), and the nonintubated patients had fewer night-time awakenings (Nishikimi et al. 2018), all suggesting this is a promising intervention, apparently without substantial CNS or other adverse effects. Lack of availability in some countries currently limits utility.

Dexmedetomidine

Dexmedetomidine, an alpha-2 agonist, produces sedation in critically ill patients by a mechanism distinct from propofol and benzodiazepines. Unlike these drugs, it increases the proportion of N3 sleep (Akeju et al. 2018). In a study of 76 postoperative non-ventilated non-cardiac surgery high dependency unit

(HDU) patients aged ≥ 65 years, very low dose dexmedetomidine (0.1 mcg/kg/hr) increased the proportion of N2 sleep from 15.8% (IQR 1.3-62.8%) with placebo to 43.5% (16.6%-80.2%), prolonged total sleep time, and improved subjective sleep quality (Wu et al. 2016). In a larger subsequent trial, the same investigators found the same protocol associated with significantly improved subjective sleep quality, along with less than half the incidence of postoperative delirium (9% vs. 23%; odds ratio 0.35, 95% CI 0.22-0.54; p<0.0001) (Su et al. 2016). Survival rates were higher initially with dexmedetomidine at six months, one year, and 2 years (rate difference 5.2%, 5.3%, and 6.7%, respectively; p<0.05), but after three years the difference was not significant (32.6% vs. 34.9% mortality; hazard ratio 0.87, 95% CI 0.68-1.13; p=0.303) (Zhang et al. 2018). In contrast, a study of 100 initially delirium-free critically-ill patients randomised to 0.2-0.7 mcg/kg/hr dexmedetomidine at night vs. placebo found dexmedetomidine associated with less delirium (relative risk, 0.44; 95% CI, 0.23-0.82; p=0.006), but no observable difference in sleep quality on a subjective sleep questionnaire (Skrobik et al. 2018). This led the PADIS guideline authors to be circumspect in their recommendation, stopping short of recommending dexmedetomidine for sleep alone but noting its potential benefit on sleep could be considered when choosing a sedative if one was indicated (Devlin et al. 2018).

Zolpidem, zopiclone, zaleplon, eszopiclone

Conveniently grouped as "z-drugs", zolpidem (an imidazopyridine), zopiclone and eszopiclone (cyclopyrrolones) and zaleplon (a pyrazolopyrimidine) are non-benzodiazepine agonists of the $GABA_A$ receptor. They are claimed to have fewer adverse effects than the commonly-used sedative-hypnotic benzodiazepines (typically temazepam, diazepam and lorazepam), although there is little evidence for this. Perhaps for this reason, there has been almost no research on these drugs as ICU sedatives, and they rarely appear in critical care guidelines, including the 2018 PADIS guidelines (Devlin et al. 2018). Perhaps their only indication is to continue chronic use (in preference to abrupt withdrawal) in a patient planned to stay only briefly in the ICU.

Amitriptyline

Amitriptyline is not covered in the 2018 PADIS guideline (Devlin et al. 2018) and is recommended against by some authors on the grounds that it has "not been studied for use in insomnia and has important potential side effects including hypotension, arrhythmias, and anticholinergic syndrome. Use … to promote sleep has been discouraged by an NIH consensus panel on chronic insomnia" (Kamdar et al. 2012). However, chronic insomnia is quite different to brief treatment in ICU, and the doses usually prescribed (10-50mg nocte) are most unlikely to cause the listed complications, especially when patient weight and metabolic function are considered. Amitriptyline, the tricyclic antidepressant most commonly used as a nocturnal sedative, is generally recognised to reduce REM sleep, but to reduce sleep latency and to increase overall sleep time (Wilson and Argyropoulos 2005). Whether this provides benefit in an individual patient is readily appreciated after only 1-2 nights' treatment. While non-pharmacological treatments are always better first-line options, given the known adverse effects of benzodiazepines and the absence of other good options, some argue that amitriptyline is a reasonable alternative.

Mirtazapine

Mirtazapine, an atypical antidepressant with a mechanism that includes presynaptic alpha-2 negative feedback blockade, postsynaptic serotonergic ($5HT_2$ and $5HT_3$) blockade, and enhanced noradrenergic and $5HT_1$ neurotransmission, also causes somnolence as a side effect that has been used as a primary indication in some patients. Its effect on sleep in patients with major depression is more encouraging than what is known of amitriptyline: it increases total slow wave sleep and REM sleep, as well as improving insomnia scores (Shen et al. 2006). As for amitriptyline, its use in critical illness is essentially not studied, but doses of 15-30mg should be safe, and n-of-1 trials in individual patients would appear to be a reasonable strategy in the absence of large randomised trials.

Trazodone

Trazodone, a tetracyclic antidepressant, is commonly prescribed to outpatients as a treatment for insomnia as an alternative to benzodiazepines. This practice was recently supported by a systematic review of 45 studies (Jaffer et al. 2017). Its off-label use (at 50mg nocte for at most 7 days) was recommended in a 2006 guideline from the UK Intensive Care Society as an alternative to benzodiazepines, although there are no trials in this context (Borthwick et al. 2006).

Antihistamines (diphenhydramine, doxylamine)

Diphenhydramine (25-50mg nocte) and doxylamine (25mg nocte) both reduce sleep latency and increase total sleep time (Koski 2011). However, a quoted 70% increased risk of cognitive decline in a cohort study comparing hospitalised patients receiving diphenhydramine to those not receiving it, along with more behavioural disturbances (Agostini et al. 2001), have led to recommendations against the use of sedating antihistamines as nocturnal sedatives in hospitalised patients. While this is not trial evidence and these adverse effects could be the result of many cofounding influences, availability of the alternatives listed above argue against using antihistamines as first-line options in adults.

Conclusion

Facilitating sleep at night is likely to have outcome benefit in many patients, and is also likely to address the insomnia that many commonly recall as a particularly distressing memory of their ICU stay. The non-pharmacological approaches to insomnia are almost always preferable first-line alternatives in critically ill patients. There is evidence that achieving the outward manifestations of sleep through use of benzodiazepines or other GABA-ergic drugs has a net detrimental effect. There are several non-GABA-ergic alternatives that show promise, but none has convincingly shown benefit in randomised controlled trials. In part, this is due to the practical difficulties of objectively measuring sleep in critically ill patients. "N of 1" trials of certain agents until the optimal approach is found for each individual might be the best strategy, in anticipation of future definitive trials. ■

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Cancer patients in the intensive care unit

Recent advances and new challenges

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It has been thought for years that cancer patients have not benefitted from intensive care unit (ICU) admission when they suffer from severe and potentially reversible acute illnesses. Fortunately, numerous studies have shown that this is not the case. Today, the number of cancer patients in ICUs around the world is increasing every year, and both survival and quality of life are improving in the same manner. This progress is due to multiple factors, from progress in anti-tumour treatments to better management of patients in the ICU.

We are moving towards an individualised and dynamic treatment that will be adapted to the type of tumour and the patient's immune response. The prognosis of the critical cancer patient is time-dependent and therefore ICU intensivists must face the challenge of making a good selection of patients with early admission and effective diagnosis and treatment.

Oncological and haematological disease is one of the leading causes of morbidity and mortality in the world (Azoulay et al. 2013). The percentage of cancer patients in ICU varies between 6% and 20% (Bos et al. 2015; Shimalbukuro-Vornhagen et al. 2016), in many cases lower than that of other less prevalent pathologies. Approximately 50% of these admissions are due to surgical procedures, while the other 50% is related to medical causes, with only 3.3% corresponding to specific causes of oncological disease (Puxty et al. 2015).

Considering that cancer treatments have increased their efficacy, associated with better prognosis and increased life expectancy, it is foreseeable that the number of cancer patients requiring admission to ICU will continue to increase in the coming years, constituting a field of compulsory continuous training for intensivists.

Observational studies have shown an improvement, not only in terms of mortality, but also in terms of the quality of life of cancer patients who have required admission to the ICU. However, this is still noticeably worse than that of the general population, both at 3 and 12 months after hospital discharge, especially in haematological patients. Old age, poor functional status prior to admission to the ICU, and a higher degree of multi-organ failure during the ICU stay are independent predictors of poorer quality of life.

In our area, we now have available a recent study series that includes a mixed population of onco-haematological patients admitted to ICU, with 36% mortality and 40% dependence on discharge (Díaz-Díaz et al. 2018). A study conducted in France showed similar clinical outcomes, with hospital mortality rates, 3-month mortality and one-year mortality of 39%, 47% and 57% respectively (Azoulay et al. 2013). These results are far removed from the classical studies, which presented unacceptably high mortalities that did not justify aggressive management of these populations (Hauser et al. 1982).

The improvement in the prognosis of cancer patients in ICU is undoubtedly multifactorial. Knowledge of these factors is fundamental to patient management and a challenge for future improvement. We can highlight five key elements:

1) New anti-tumour therapies

The medical and surgical treatment of cancer patients has changed considerably. Chemotherapy in ICU, unthinkable until relatively recently, may be a therapeutic option in selected critical patients. Treatment increasingly targeted at tumour cells as evidenced by immunotherapy (monoclonal and bispecific antibodies (BABs), chimeric antigen receptor (CAR) T cells, and checkpoint inhibitors) is, in general, effective and well tolerated. These therapies have also led to the appearance of new complications associated with the treatment that the intensivist must know about and treat, such as cytokine-release syndrome, which can simulate sepsis or anaphylaxis and whose treatment can be very different.

Laparoscopic (keyhole) surgery has decreased the time and postoperative complications of many tumours. Even the most aggressive techniques such as cytoreductive surgery and heated intraperitoneal chemotherapy require a short stay in ICU when performed by experienced teams.

2) Criteria for admission to ICU

We are getting a better selection of patients who can benefit from admission to the ICU. This is due to, among other reasons, greater collaboration by oncologists, haematologists and intensivists, with the development of management protocols and agreements on admission criteria (Carmona-Bayonas et al. 2018).

The decision whether or not to admit a cancer patient to the ICU is a difficult one, and both the potential benefit and the possibility of the treatment being unsuccessful should be taken into account. The admission of an oncology patient to ICU should be based on three principles:

- The reason for admission must be reversible
- The patient shows an adequate quality of life and the prognosis of the oncological disease and its therapeutic possibilities justify the use of aggressive measures
- The patient or his/her family members do not refuse admission.

The prognosis of cancer patients in the ICU, as well as those with non-oncological conditions, depends on the performance status, the severity of the acute illness and the number of organ systems that fail. Oncological diagnosis, the stage of the tumour, neutropaenia, aplasia or the presence of metastasis have little or no relevance to the short-term prognosis of a cancer patient in ICU. In general, cancer patients have a worse prognosis than non-cancerous patients in ICU, especially those with haematologic malignancies. This is probably due to being an immunocompromised patient and not having cancer "per se." If we could determine the immunosuppression status of critical patients in routine clinical practice, we would see a good correlation between that status and the prognosis. Over the next few years, the increased knowledge of the immune response in critical cancer patients, the possibility of obtaining real-time data and the possibility of therapeutically modulating this response will represent an unprecedented advance in improving survival.

Traditional prognostic scores have very limited value in cancer patients and only scores that assess organic function (sequential organ failure assessment [SOFA], Logistic Organ Dysfunction Score [LODS]), better predict mortality and are useful in making decisions. The short-term prognosis is mainly associated with the number of dysfunctional organs (especially if more than 3), the need for invasive mechanical ventilation (IMV) and the need for renal replacement therapy.

3) Speed and precision

Cancer patients have varying degrees of immunosuppression, making them more likely to have conditions, not just infectious ones, during their illness and to respond negatively to these complications. Even minor organ dysfunctions have been associated with an increase in mortality, thus making early admission to the ICU a better prognostic determinant (Legrand et al. 2012). It is especially relevant when the oncology patient is admitted to the ICU with sepsis or acute respiratory failure (Hanzelka et al. 2013; Mokart et al. 2013). In high-risk patients we should consider the risk/benefit of preventative admission to ICU.

> **"why not a *code cancer* if we have to be especially precise and quick in our diagnostic and therapeutic response to cancer patients?"**

The speed with which the appropriate treatment is put in place will have a significant influence on prognosis. The creation of extra-ICU rapid response teams, extra-ICU patient assessment teams or specific projects for certain pathologies (sepsis code) has led to progress in this area.

In a large number of critical cancer patients we do not have a reliable diagnosis and these patients have a worse prognosis. Noninvasive or minimally invasive diagnostic techniques such as computed tomography (CT), lung and heart ultrasound, haemodynamic monitoring by thermodilution and/or pulse wave analysis and early analysis of samples taken by bronchoscopy (bronchoalveolar lavage and tracheal aspirate) should be the cornerstone of early diagnosis.

In the group of acute time-dependent pathologies in which an improvement in prognosis has been demonstrated with rapid action protocols: code myocardial infarction, code stroke or code sepsis, there are also complicated oncology patients. Why not a *code cancer* if we have to be especially precise and quick in our diagnostic and therapeutic response to cancer patients?

4) Improving support measures in ICUs

This is especially true for respiratory support, both noninvasive mechanical ventilation (NIMV) and high-flow nasal cannula oxygen (HFNC). The need for tracheal intubation and IMV has been considered the main risk factor for short-term mortality in onco-haematological patients admitted to the ICU. Despite the improvement in survival due to the application of protective mechanical ventilation, and based on different clinical studies (Squadrone et al. 2010; Lemiale et al. 2015), NIMV has been recommended as the initial treatment for respiratory failure in these patients, since it significantly reduces the need for tracheal intubation and IMV, avoiding its associated complications and improving prognosis.

However, a new multicentre study (Lemiale et al. 2015) was published in 2015, including the largest number of patients to date, which sought to demonstrate the possible beneficial effects of NIMV on this population of patients. Despite the criticism received (less severe acute respiratory failure based on lower respiratory rate, low mortality of the sample, few hours of NIMV) the study found no significant clinical differences when using NIMV as a first therapeutic possibility. In both branches of this study, HFNC was used in nearly 40% of the cases, which allows us to hypothesise whether the best approach for these patients is a joint use of both systems.

In recent retrospective trials (Mokart et al. 2015), this approach has been associated with a reduction in mortality, although it is necessary to wait for the results of new clinical studies before drawing definitive conclusions. In any case, and as the study by Kangelaris et al. (2016) highlights, it is important to remember that in patients who choose a noninvasive ventilatory strategy, and

The critical oncology patient in almost ten phrases
Adapt to our environment
Teamwork and multidisciplinary work
New therapies and better prospects. New complications
Early or advance admission. *Code cancer*
Rapid diagnosis and treatment
Individualised and dynamic decisions
ICU Trial. Avoid "all or nothing" criteria and measures
Humanization
Quality of life and quality of death

who subsequently require tracheal intubation, mortality is significantly higher in both the short and long term; therefore, we should not delay invasive support in the case that it is required.

5) ICU trial

In the group of patients about whom we have questions as to the attitude to be taken, it would be advisable to carry out an ICU trial, this being understood as admission to the ICU without therapeutic restrictions for at least 72 hours, with frequent and periodic re-evaluations, with the intention of not perpetuating unnecessary treatments and prolonging the suffering of the patients and their families.

The ICU trial is based on a study published by Lecuyer et al. (2007), in which they found no statistically significant variables at the time of admission to the ICU that differentiated between survivors and non-survivors. However, after 72 hours none of the patients who required increased organ support measures survived. Thus, if after that time, the patient experiences failure of 3 or more organs or worsening of the previous multi-organ failure, vital expectations are minimal and it would be advisable to establish measures to limit the therapeutic effort (Prieto del Portillo et al. 2014).

Thus, not only do we avoid unnecessary treatment or suffering of family members, but we will also participate in the prevention of conflicts between ICU staff members and the emergence of burnout syndrome (Piers et al. 2011).

Admission to ICU does not necessarily imply taking all necessary measures for as long as possible. We must take into account a wide range of possibilities. We can admit patients with the intention of giving unrestricted treatment for at least five days and reassess it according to its evolution. We can enter for haemodynamic or renal support and limit IMV. We can even check in to optimise comfort measures or reduce dyspnoea with high-flow nasal goggles or IMV for patients with poor prognosis. Here, too, decisions must be made in a multidisciplinary manner (intensivists, oncologists and haematologists) and in agreement with the patient and family members.

All therapeutic options can be considered and individualised, including those that have traditionally been considered limiting factors, such as chemotherapy in ICU or extracorporeal membrane oxygenation (ECMO) in patients with severe refractory respiratory failure. Subgroups with poorer prognosis, such as patients with severe allogenic bone marrow transplant and graft versus host disease (GVHD) or patients with lung neoplasms requiring mechanical ventilation for respiratory failure and who may require chemotherapy in ICU, may also benefit from admission to ICU.

Conclusions

For many years ICUs have focused on the treatment of acute illness and neglected the emotional side of patients and families. This is most evident in cancer patients. We must humanize ICUs, make them open to family members, minimise noise, integrate psychologists into our work teams, respect the circadian rhythm of patients and make the environment less inhospitable and more hospitable.

We are moving towards individualised treatment for cancer patients and this also requires us to adopt individualised and dynamic support measures. Admission criteria and therapeutic measures in ICUs should no longer be "all or nothing" and should be adapted to each patient and their wishes. The ICU must also be able to provide quality at the end of life. Undoubtedly, the human and technical resources available to us vary greatly between centres and countries, so we must also adapt to our working environment.

Conflict of interest

Isidro Prieto del Portillo declares that he has no conflict of interest. Ignacio Sáez de la Fuente declares that he has no conflict of interest. Ignacio Pujol Varela declares that he has no conflict of interest. ■

Abbreviations

HFNC high-flow nasal cannula oxygen
IMV invasive mechanical ventilation
NIMV noninvasive mechanical ventilation

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What should we stop doing in the ICU?

In this article, I highlight that the most important thing intensive care physicians should stop doing is ignoring that they are prone to several cognitive biases. I will first support my statement by looking for conceptual caveats and cognitive bias in routine intensive care unit (ICU) care, and then move to specific patient and structural problems.

Intensive care is an interesting specialty. From all the early excitement in the 1970s, passing through two decades of intensive physiological use at the bedside, intensive care landed on the rough ground of modern randomised controlled trials (RCTs) in the late 1990s and early 2000s. The increasing number of critically ill patients coupled with new monitoring devices and important funding both from governmental and private agencies (including pharmaceutical companies) fostered research. In the early 2000s, the panorama looked promising, with positive trials coming out on a frenetic basis (Bernard 2001; Rivers 2001). Regrettably, the initial enthusiasm was followed by a wave of negative results (Ranieri 2012; PRISM Investigators 2017). Many interventions that seemed promising in the early 2000s were sequentially disproved or proved to be harmful, which has been the basis for the rationale of limiting excesses of interventions and treatments in the critically ill, the so-called "doing less" (Singer 2006).

What are the conceptual caveats in routine ICU care we should stop doing?

This section could be summarised in one sentence: Obtain less (not more) data and reduce treatment exposure considering it part of the disease and not of the healing process. Do so because we are all prone to cognitive bias.

The first part of the sentence brings a concept that is well-known to experts in behavioural science: information overload (Bawden 2008). Excessive information is known to reduce accuracy and increase confidence in the decision-making process (Hall 2007). This association can have disastrous consequences for critically ill patients, worsening the performance of important acute decisions and making physicians less prone to notice their own mistakes.

As the heart might be responsible for generating its own afterload, intensivists are also partially responsible for generating their own *information* overload. Examples include excessive use of haemodynamic monitoring in otherwise stable patients, pleiads of routine laboratory and imaging tests and inputs from several colleagues and healthcare workers (Manor-Shulman 2008). In the eagerness of having a quick diagnosis and treatment, intensivists generate data that will only aggravate the problem. Coupled with the increasing difficulty in accessing patient´s data due to poorly designed electronic health records, this creates an intensivist that has both information overload *and* information anxiety; that is, an individual exposed to too much data and that has trouble trying to access it (even the parts that indeed matter!). This results in a nightmare that is well known by most of us. A vignette is shown in **Figure 1**.

In the left part of this example, a series of types of cognitive bias occurred, triggered by a spurious elevation in C-reactive protein (CRP) levels that were routinely collected. Due to concerns of an untreated infection, the physician tries to find something that suits his/her keenness to explain the labora-

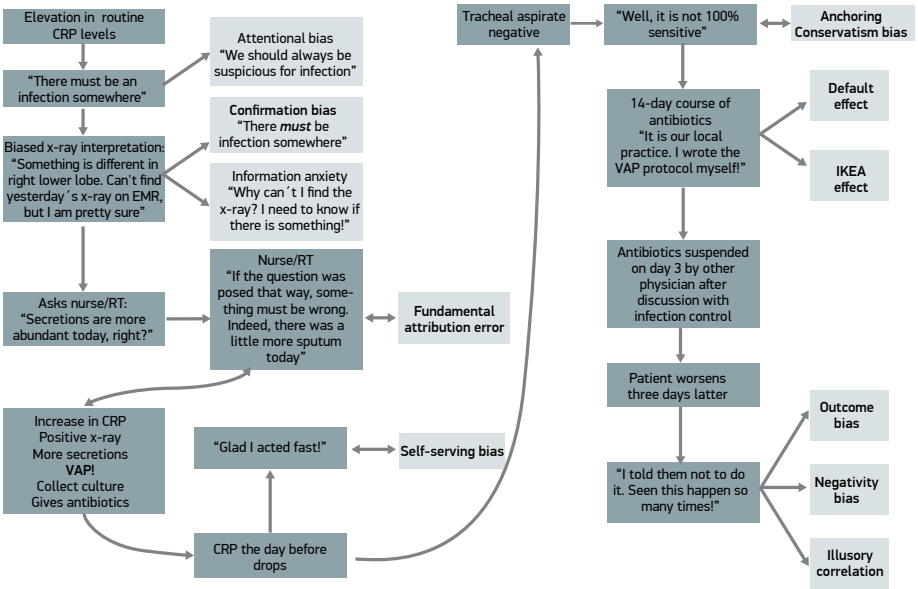

Figure 1. Spurious elevation in CRP levels in a stable patient on mechanical ventilation

CRP C-reactive protein EMR electronic medical record RT respiratory therapist VAP ventilator-associated pneumonia

Table 1

Practice	Comment	Cognitive bias involved	Suggestion	Reference
		ICU STRUCTURE		
ICUs built in improvised spaces with old-fashioned architecture	There is no place for old-fashioned windowless ballroom ICUs in modern practice. Natural light deprivation is a real issue.	Conservatism; default effect.	New ICUs should be designed to improve patients and staff wellbeing. This includes windows, places to interact with staff (cafeterias), proper resting rooms, family meeting rooms, etc.	Caruso 2014; Mroczek 2005
Keep families outside the ICU	Family engagement may reduce delirium and improve outcomes.	Conservatism; default effect; hostile attribution bias.	Adopt liberal visitation policy while coping with staff´s own demand for privacy.	Soares 2017
Keep pets outside the ICU	There are few plausible reasons to keep pets outside the ICU. There are many potential benefits for patients and staff.	Conservatism; default effect; "not invented here" bias.	Adopt a more liberal pet visitation policy in ICUs.	Hosey 2018
Ignore staff´s own health	Burnout is endemic in practitioners. Ignoring staff burnout can harm staff and patients.	Identifiable victim effect; Ostrich effect.	Recognise the problem. Attempt to treat burnout as an organisational problem and *not* an individual issue.	Ricou 2018
		DAILY CARE		
Daily chest x-rays	Increases radiation exposure. May worsen several biases due to poor method sensitivity/specificity.	Conservatism; default effect.	Switch to on-demand methods such as ultrasound (if available) or more selective x-ray prescription.	Resnick 2017
Daily full set of exams	May produce noise without clear benefit. May increase need for transfusions.	Conservatism; default effect; bandwagon effect.	Adopt a minimal daily set of tests; add tests as indicated.	Zimmerman 1997
Widespread contact precautions	May be useful for Gram-positive bacteria but data lacking for multidrug-resistant Gram-negative. Widespread use can increase adverse events at patient level.	Conservatism; default effect; continued influence effect.	Join randomised controlled trials on contact precautions. Consider local study.	Furuya 2018
Aggressive antibiotic use after infection suspicions in stable patients	For stable ICU patients, a wait-and-see approach may result in better outcomes than an aggressive strategy.	Conservatism; default effect; continued influence effect; Semmelweis reflex.	Adopt more conservative triggers to start antibiotics in stable patients.	Melsen 2013
Long pre-established courses of antibiotics	Shorter courses of antibiotics are probably safe, reduce costs and antibiotic exposure.	Conservatism; default effect; Bandwagon effect; Semmelweis reflex.	Consider strategies to reduce length of antibiotic courses.	Klompas 2017; Sawyer 2015
Alveolar recruitment for ARDS	Increased mortality in large RCT.	"Not invented here" bias; Semmelweis reflex.	Apply evidence as it stands.	Cavalcanti 2017
Aggressive hypothermia protocols	Failed to improve outcomes in most scenarios.	Semmelweis reflex.	Consider switching to normothermia protocols.	Shaefi 2016
Aggressive glycaemic control protocols	Associated with more adverse events, no benefit for clear majority of patients.	Semmelweis reflex.	Adopt more liberal glycaemic control.	Finfer 2009
Early aggressive nutrition protocols	While no clear harm can be attributed, it may derive attention from more pressing problems.	Semmelweis reflex.	Adopt timely introduction of nutrition to the most severely ill patients.	Casaer 2011
Proton pump inhibitors prophylaxis for upper gastrointestinal bleeding	May not be useful and may increase complications.	Conservatism; Semmelweis reflex.	Probably not necessary. Large RCT recently completed.	Krag 2016
Early goal therapy for sepsis	Large bulk of evidence suggesting it may increase costs due to more ICU admissions without clear mortality benefit.	Semmelweis reflex.	Focus on early diagnosis and source control in septic patients (preferably outside the ICU).	PRISM Investigators 2017
Use fluid bolus to treat every conceivable abnormality (oliguria, hypotension, tachycardia, reduction in consciousness levels, etc.)	Fluid creep is a major issue. Fluids should be considered drugs with very low therapeutic range.	Law of the instrument ("Give a small boy a hammer, and he will find that everything he encounters needs pounding", Maslow 1966); conservatism; Semmelweis reflex.	Reduce fluid creep starting with maintenance fluids and reducing unnecessary dilutions. Adopt early negative fluid balance whenever possible.	Van Regenmortel 2018
Attempt to correct physiological abnormalities	Physiology can be bent to fit one´s desire for adequacy. There is no single or correct physiological parameter in critically ill patients.	Conservatism; default effect; continued influence effect.	Aim for physiological targets only in the absence of hard evidence.	Reade 2009; 2013

tory finding and somehow slack his fear of negligence. Secure physicians would probably ignore (or would not even have ordered) CRP levels and would choose a "wait-and-see" approach (Hranjec 2012). However, some physicians would embark on a destructive cycle of cognitive bias aiming at confirming their hypothesis. A similar scenario is conceivable for an apparently stable patient, who presents with an elevated lactate level, low central venous oxygen saturation etc. The problem, therefore, is the attempt to contextualise excessive information inside an otherwise unremarkable situation.

It may be stated that simply collecting *less* data is a childish suggestion and that all efforts should be made to use *more* data to improve treatment. I beg to disagree. A probabilistic interpretation of data is well suited in complex scenarios when we are accustomed to information (this applies to most Bayesian inference done in medicine); however, when data is new, time is short, and a decision is crucial, approaches that minimise choices based on less data may outperform complex models (Hardman 2003). This applies to many busy strained ICUs around the world.

Now let´s move to the right part of **Figure 1**. Damage has been done and our patient with a spurious irrelevant CRP elevation now has a ventilator-associated pneumonia (VAP) diagnosis. VAP has a doubtful attributable mortality but appears to be associated with prolonged mechanical ventilation and, obviously, higher costs (Melsen 2013). A VAP diagnosis leads to serious developments, such as antibiotic exposure, family distress ("Now, above all, he has a pneumonia!") and even administrative issues (billing and benchmarking). Cognitive bias will not stop there. Despite evidence that guiding antibiotic time using CRP and/or procalcitonin levels are appropriate (de Jong 2016), the physician may now choose to embrace a conservative approach and apply a whole two-week course of antibiotics (the *default effect*). The same physician that relied on CRP to diagnose VAP is now shaky to stop antibiotics when CRP drops. However, if CRP dares to rise again in the following 48 hours, it is inevitable that concerns about "treatment failure" will arise and the circle of overtreatment will prevail. If physicians would consider that treatment is *part* of the disease and not an indissociable part of recovery, maybe the pros and cons would favour the first. In fact, using our infection vignette as an example, it is estimated that up to 20% of all patients receiving antibiotics will develop a serious adverse reaction (Tamma 2017). Maybe net benefit would be negative in our vignette?

> **"in the eagerness of having a quick diagnosis and treatment, intensivists generate data that will only aggravate the problem"**

The right side of the figure continues with a well-known sequence of cognitive biases that preclude proper patient management. The physician becomes emotionally tied to the diagnosis, knotted to the VAP protocol he wrote for the ICU (the "IKEA effect", Norton 2012) and will fail to see evidence contrary to his hypothesis. If antibiotics are withdrawn in the next days by other physician and the patient eventually worsens, this will only further close the book on cognitive bias. While I used VAP for this example, the reader might find it suitable for many haemodynamic interventions (including the fluid bolus-diuretics conundrum, cardiac output measurements, etc).

Moving to the patient level

After the vignette, I hope that the reader considers that a more pragmatic approach to intensive care may be desirable. The cornerstone is transposing one of the Orwellian rules of writing to the ICU: "If it is possible to cut a word out, always cut it out" (Orwell 2013). Let´s replace "word" for "treatment" or "practice" and see what we can do. Examples are shown in **Table 1**.

For each intervention, procedure and treatment shown in **Table 1**, one cognitive bias will have to be overthrown. This is not an easy process, since most of the teaching in medicine is indeed based on passing bias and abstract concepts from generation to generation. It is commonplace to hear that we should aim to keep a patient "normovolaemic", "well-nourished", etc., while it remains underappreciated that these terms are closer to a linguistic trick than to a medical practice. The first step to embrace a modern ICU is understanding that much of what we did and believed was part of habit and not science. This is the very reason why conservatism, Semmelweis reflex (Leary and Wilson 1991) and default effect are the most frequent cognitive bias shown in **Table 1**.

In the dawn of civilization in ancient Eridu, architects were more interested in rebuilding structures from scratch than preserving previous buildings. The Eridu fortress was rebuilt eleven times. As Paul Kriwaczek stated, ancient Eridu habitants were impatient with what was old and receptive to the new (Kriwaczek 2012). Intensive care should remember its roots but allow the new to be built upon its ground. ■

Abbreviations
CRP C-reactive protein
ICU intensive care unit
VAP ventilator-associated pneumonia

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Caring for very old patients in the ICU

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Describes the epidemiology and outcomes for very old patients as known in 2018, along with a short introduction to the most relevant "geriatric syndromes" important also for intensivists, and discusses where we should increase our body of knowledge to make a more precise triage in this patient group.

The very old ICU patient is a term often used for those patients aged ≥ 80 years. This group of patients constitutes 10-15% of today's ICU patients in Europe, and is expected to rise in absolute and relative terms in parallel with the increase of life span in our countries. If we continue to have the same policy towards treatment of the critically ill very old for the coming 25 years, we may well see a doubling of this patient group. Even today there is an ongoing discussion about who to treat, when and where to treat these patients, and arguments span from not to consider age at all, to question the admittance of the very old in general. Most researchers and clinicians argue there must be a middle way, allowing for active treatment in selected patients, while on the other hand reducing the treatment intensity, maybe to comfort and care, in others.

The problem is obvious: how to select those that will profit from intensive care from those that most certainly will not? This is of course a generic challenge intensive care has had for decades, and we hoped the traditional severity scoring systems could offer us help. However, these systems have not been found accurate enough to guide decisions at the individual patient level, although they may perform well on a group level. They have also been found to perform less well in ICU-subpopulations, like in the very old (Minne et al. 2011).

Epidemiology

We are not sure if the absolute increase of patients ≥ 80 years we observe in many ICUs really is parallel with the increase in the elderly population per se. We know the elderly population is increasing in European countries as well as in the rest of the world, but very few studies adjust the increase in elderly ICU admission to the increase in the general population. This was recently done in Scotland where they in fact found the admission rates among the elderly (≥80) to decrease over time from around $37/10^5$ in 2005 to $29/10^5$ in 2009, a *reduction* of 22%! (Docherty et al. 2016) They speculate whether this reduction can be rationing based on chronological age, selecting less morbid elderly patients, but no data was revealed to support this assumption.

Outcomes

Several studies about short- and long-term mortality in very old ICU patients have been published over the last 15 years. Lately also some large prospective multicentre studies have been performed, mainly to determine survival, but also quality of life (QOL). **Table 1** summarises results from three such recent studies showing that 25-35% of the very old die within a month. In the Canadian study, also QOL of one-year survivors was studied, indicating that approximately 50% of the patients that survived to one year (≈50%) had significantly reduced QOL.

Geriatric syndromes

Geriatric medicine has for decades used a "battery" of age-related assessments found to be very relevant with advancing age. For some time, many of these assessments also have found use outside traditional geriatric medicine, in particular for surgical procedures. Lately some of these syndromes, particularly frailty, have also been used to describe ICU cohorts.

Frailty

With frailty, we understand the gradual decline in various body functions that occurs with age, and manifests itself as diminished reserves during stress. It is important to underline two important facts with frailty:

1. Frailty does not always parallel chronological age; hence we can find frailty in ICU patients not considered to be aged, and we can find patients with a high chronological age without being frail.
2. Frailty is not a disease, and must be separated from such, although the border between frailty and disease is sometimes difficult to define.

Typical frailty symptoms may include (but are not restricted to):

- Slow walking speed
- Reduced activity level
- Exhaustion
- Decreased muscle mass and strength
- Unintentional weight loss

There are several methods to identify frailty. Such assessment is usually based on one of two different assessment methods: Fried criteria and Rockwood methods. The former is often called frailty phenotype, and the latter frailty index. The phenotype is based on a pre-defined set of criteria (categorical variables), while the frailty index is a result of a clinical evaluation using continuous variables and a more unspecified

set of criteria (Cessari et al. 2014). Since both methods have clinical disadvantages, particularly in the acute care setting, a new clinical frailty scale (CFS) was developed in Canada in the second part of the large Canadian study of health and ageing (Rockwood et al. 2005). The last version of CFS includes a 9-scale partly visual and partly descriptive scale and has gained popularity in situations where patients are unable to participate. Several large prospective studies have been conducted in recent years using the CFS, showing very good correlation between frailty and outcomes in the very old population of critically ill patients. In the large *Very Old Intensive Care Patient: A Multinational Prospective Observation Study (VIP1)* study of more than 5000 elderly ICU patients in Europe, frailty was found to be an important and independent factor for 30-day mortality, with a near linear relation between increasing frailty and mortality (Flaatten et al. 2017).

Sarcopaenia

Sarcopaenia is the specific name for muscle wasting in the elderly. It is an important cause of functional decline and is interwoven with frailty. Occurrence of sarcopaenia is very common. It is found in 11-50% of elderly people > 80 years and is associated with a negative outcome in a variety of studies. There are multiple causes of sarcopaenia, and inactivity is probably the most important one, although malnutrition and inflammation also may play a role. Commonly it can be diagnosed using imaging techniques like MRI, CT and ultrasound, but more often simpler methods like gait speed and muscle strength in the arms are used as screening tools. The European Working Group on Sarcopenia in Older People has published clinical guidelines and consensus criteria for age-related sarcopaenia (Cruz-Jentoft et al. 2010). Here gait speed < 1 m/s in a 6-metre course and handgrip strength < 30 kg in men and < 20 in women may indicate sarcopaenia.

> **"frailty was found to be an important and independent factor for 30-day mortality"**

In intensive care these methods to document sarcopaenia are difficult, since both gait speed and handgrip strength require awake and cooperative patients. However, it may have a role at discharge and post-ICU follow-up. Since sarcopaenia at admission adds to ICU-acquired loss of muscle mass (inactivity and stress-mediated catabolism) the net result may be detrimental for the very old with regards to post-ICU rehabilitation. Hence methods to prevent further muscle mass in critically ill sarcopaenia patients are vital.

Recently, studies using ultrasound measurement to diagnose sarcopaenia have been published and may provide a fast, noninvasive method to document muscle mass at admission that can find its way into initial assessment of elderly ICU patients.

Cognitive decline

Age-related cognitive decline is understood as a normal (non-disease related) ageing of cognitive functions. It does not affect all elderly people, but mild cognitive impairment (MCI) is a frequent finding in the elderly and has been found in 15-20% of people aged 65 and above. It may affect primarily memory (amnestic MCI) or other thinking skills, known as "non-amnestic MCI". A detailed mapping of cognitive function takes time and requires a cooperative patient. There are quick methods like mini-mental state examinations that are often used to screen for dementia, but these also require awake patients. However, a simple questionnaire designed to ask close relatives about their next-of-kin's mental state is available and can be used also in emergency settings. It is called IQCODE: the informant questionnaire on cognitive decline in the elderly (Jorm et al. 1989). Here an informant who knows the patient well is asked a series of questions about mental state, and compares present status (before the illness) with 10 years ago. Although not as sensitive as direct examination of the patient, it is a quick screening tool and may have relevance for rehabilitation and cooperation with the patients while in the ICU.

Immunosenescence

Our immune system is affected by age. Immune cells are continuously renewed from stem cells. Both the proliferative capacity and the number of these immune cells are decreased due to progressive telomere shortening, resulting in an immune dysfunction

Table 1. Results of three large prospective multicentre studies in the very old ≥80 years

Author	Years conducted	Number pts	Number countries (ICUs)	ICU mortality	One-month mortality	6-month mortality
Heyland et al. 2015	2009-13	1671	1 (24)	22 %	35 %	
Flaatten et al. 2017	2016-17	5021	21 (311)	22.1%	32.6%	
Guidet et al. 2017	2012-15	3037	1 (24)		25.6%	41.9

over the years, which is called immunosenescence. This may explain the increased susceptibility in elderly people to acquire infections, clearly demonstrated with the markedly increased incidence of sepsis in the elderly population. Unfortunately, tests for immune function are at present not fully developed, and we lack a quick and reliable method to identify patients at risk.

Specific ICU care for the elderly

Studies have repeatedly shown that the elderly patient is given less active treatments compared with their younger counterparts. The reasons for this are not clear, but may imply therapeutic nihilism. This is of course unfortunate, since when admitted, all patients should be given appropriate care until a decision of limitation eventually is chosen. The potential to involve a geriatrician in the ICU team is also attractive. Elderly patients usually come with a lot of "baggage": co-morbidity and associated drug therapies. A study from nursing homes (Barber et al. 2009) revealed that on average the residents used 8 different medications daily. Not all of them are necessary, and some may be potentially harmful in the ICU setting. To help sort this out a geriatrician can be of help. Geriatric competence may also be helpful in working out the best plan for rehabilitation in very old ICU survivors.

The response to ICU therapy is important and should be evaluated as soon as possible after admission. For this daily organ failure assessment is important, and responders should show improved function within some days. If this does not occur or failure increases, most would then consider further ICU treatment questionable. Withholding or withdrawal of care should be considered and discussed with caregivers or family. Many of the patients would then be offered comfort and care instead of intensive care.

Delirium is frequent in the very old, and is the rule more often than not. Hence the ICU should be prepared, and avoid known factors that increase delirium: heavy sedation, particularly use of benzodiazepines; ensuring sleep at night and that patients are awake and mobilised at daytime, even if still on a ventilator, are also important factors. Further muscle wasting and malnutrition should also be focused on.

> "the potential to involve a geriatrician in the ICU team is also attractive"

What more do we need to know?

There are more questions than answers with regards to very old ICU patients. First and foremost, we need better prediction ability to identify elderly patients that most probably will profit from ICU admittance, and those that probably will not. We know the one-month mortality after intensive care is about 40% after acute admissions, and to identify most of them before ICU admittance should be given high priority. Not only is this important for our societies with an increasing shortage of ICU beds, but primarily for the patients and caregivers. An ICU admission is a burden for all, and should probably not be offered if most lights alert red. The search for prediction systems with a very high sensitivity and specificity may prove to be impossible. Still, we must continue to investigate this in depth, and in particular to include information from "geriatric" syndromes as specified above. The message from using frailty assessment at admission is promising. Again, in the VIP1 study we found frailty to be the best individual predictor of 30-day mortality, even better than the Sequential Organ Failure Assessment (SOFA) score at admission (Flaatten et al. 2017). It is possible that a combination of the geriatric syndromes alone or with other selected markers can give us a useful prognostic score, to be helpful in the pre-ICU triage process. The only way to find out is through large prospective studies testing the power of these new markers to predict outcomes.

Today we have simple and robust methods to map frailty, sarcopaenia and cognition before ICU admission. Hopefully also immunosenescence will be possible to assess in a simple way in the near future. ■

Conflict of interest

Hans Flaatten declares that he has no conflict of interest.

Abbreviations

CFS clinical frailty scale
ICU intensive care unit
MCI mild cognitive impairment
QOL quality of life

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The sepsis box, bag and trolley

Evaluation of aids to the delivery of sepsis treatment

In NHS Wales the Sepsis 6 bundle, delivered within one hour of sepsis recognition, has been standard treatment in acute hospital settings since 2013. We describe various methods for increasing the speed and effectiveness of Sepsis 6 bundle delivery that have been trialled with positive outcomes.

Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer et al. 2016) and is estimated by the UK Sepsis Trust to cause the deaths of at least 44,000 people in the UK annually.

Scaling the findings of a large meta-analysis (Fleischmann et al. 2016) for relative population size gives an incidence in Wales of between 8000-13,000 cases of sepsis per annum with an associated mortality of between 2200-2300.

These estimates accord with both extrapolation from an inspection of UK critical care data (Daniels 2011a) and a retrospective review of mortality within one Welsh hospital (Robinson 2013). The latter study estimated sepsis to be responsible for approximately 15% of hospital deaths.

The size of sepsis in Wales study (Szakmany et al. 2016) found a prevalence of sepsis and severe sepsis in Welsh acute hospitals of 5.5% with associated mortality at 90 days of 31%.

In NHS Wales the aim to reduce avoidable harm and mortality caused by sepsis has been a tier one Welsh Government target since 2013, and all Health Boards and Trusts have participated in the national Rapid Response to Acute Illness (RRAILS) programme since 2011.

During the time that this programme has enabled clinicians to identify and treat sepsis more quickly there has been a reduction in the numbers of deaths associated with two sepsis ICD10 codes. NHS Wales was the winner of a Global Sepsis Award in 2015 (Hancock and Watkins 2017).

An important component in this achievement has been enabling clinicians to rapidly recognise sepsis and treat using the 'Sepsis 6' care bundle.

The Sepsis 6 bundle

The original Surviving Sepsis Campaign Guidelines (Dellinger 2008) and subsequent revisions have focused on the delivery of evidence-based, time-limited 'care bundles' at various points in the patient pathway, including within 1-, 3-, 6- and 24-hour time frames.

UK healthcare has generally chosen to adopt the 'Sepsis 6' care bundle, which was first devised by Ron Daniels of the UK Sepsis Trust and the delivery of which, within a one-hour timeframe, has been shown to be associated with improved patient outcomes (Daniels et al. 2011b; NCEPOD 2015)

The six elements of the bundle are:

1. Give O_2 to keep sats above 94%
2. Take blood cultures
3. Give IV antibiotics
4. Give a fluid challenge
5. Measure lactate
6. Measure urine output

In NHS Wales the Sepsis 6 bundle, delivered within one hour of sepsis recognition, has been the accepted and standard treatment for sepsis in all acute hospital settings since 2013. Percentage compliance with delivery of the bundle is measured within all Health Boards as a key quality improvement metric.

An important function of the RRAILS programme has been to support clinicians in testing various methods for increasing the speed and effectiveness of Sepsis 6 bundle delivery. These have included the sepsis bag, sepsis box and sepsis trolley.

Description and evaluation of such tools is not well developed in the literature. One large-scale literature review of the crash cart /resuscitation trolley reported little information or uniformity in the range of equipment, instructions for use or evaluation of effectiveness (Jacquet et al 2018).

Kafle and Nath (2014) report improvements in outcomes for patients treated with a range of sepsis interventions including a sepsis box but in the context of a small sample size (n=30).

The sepsis bag

Working with 1000 Lives Improvement Service, the Critical Care Outreach Team (CCOT) at the Royal Glamorgan Hospital, Cwm Taf University Health Board, introduced a sepsis response bag in 2012. The bag contained the six elements of the Sepsis 6 care bundle with the exception of antibiotics.

The bag was evaluated by analysis of the National Early Warning Scores (NEWS) of eighty patients pre- and post receiving treatment using the bag. This analysis showed a statistically significant reduction of NEWS at 24 hours of treatment using the sepsis bag with the largest reduction being -8 (**Figure 1**).

The sepsis response bags were found to be favourably associated with the delivery of the Sepsis 6 and the reduction in NEWS was accepted as inferring a better patient outcome.

However, evaluation of the sepsis bags highlighted several difficulties:

- Infection prevention and control advice in the Welsh Government was that the bags would be impossible to clean effectively between patients.
- The bags were not sealed and equipment could be and was removed. This obviously had serious implications for completeness of the kit when the bag came to be used again.
- Once the bag had been used it was difficult to get it replenished immediately.
- The majority of the bags had been used by the CCOT and not by medical or nursing staff in the ward areas, potentially resulting in a delay in delivery of the Sepsis 6 bundle.

In order to address these issues whilst maintaining the concept of the single adjunct for delivery of treatment the 1000 Lives Improvement Service and Cwm Taf University Health Board approached an industry partner to collaborate in developing and testing a solution.

The sepsis box study

The disposable single-use box that was collaboratively developed as a result contained all the elements to deliver the Sepsis 6 apart from antibiotics. Each element was contained within a separate, sealed compartment with a perforated cardboard 'door' modelled on the idea of the advent calendar.

The box also contained all the documentation necessary for recording delivery of the Sepsis 6 bundle as well as a copy of the Health Board antibiotic formulary.

The study took place between May 2016 and April 2017 with a box being placed in all clinical areas, excluding the intensive care unit (ICU) and emergency department (ED), at two district general hospitals within Cwm Taf University Health Board. As boxes were used they were replaced by the Critical Care Outreach Team who also performed the role of data collectors. A data entry clerk transferred data to a purpose-built database and the results were analysed by both the 1000 Lives Improvement Service and Cwm Taf University Health Board.

In addition to the outcomes associated with use of the sepsis bag this study also had the aims to:

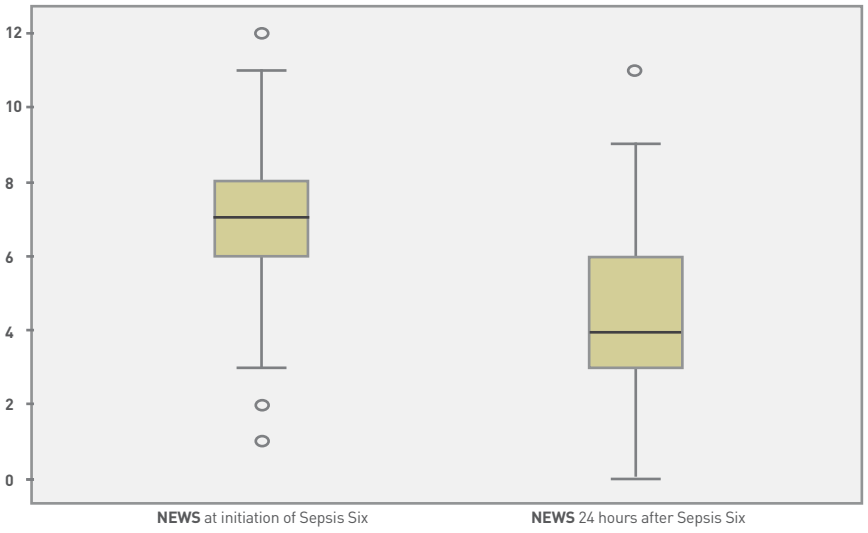

Figure 1. National Early Warning Scores (NEWS) pre- and post receiving treatment using the sepsis bag (n=80)

- Improve Sepsis 6 bundle compliance
- Engage ward staff to initiate the Sepsis 6 care bundle
- Prevent admissions to critical care.

A staff survey was carried out concurrently to evaluate attitudes to use of the sepsis box.

Results

Data was recorded for 114 patients who had been treated using the sepsis box. Members of the Critical Care Outreach Team (CCOT), partly due to an issue with the distribution of blood culture bottles to wards during the trial period, initiated the majority of boxes.

The staff survey revealed that the single-use sepsis box was generally positively regarded and was favourably associated with the delivery of the Sepsis 6 care bundle by ward staff.

Outcomes

Quantitatively, positive patient outcomes were associated with use of the single-use sepsis box. The results from the trial indicated a significant drop in average NEWS score at 24 hours and an inferred better patient outcome from use of the box (**Figure 2**). Of the 114 patients, the mean NEWS score at the point of Sepsis recognition was 7.66 indicating a high acuity and a strong mortality prediction whilst the mean NEWS score at 24 hours post treatment was 3.89.

Of the 114 patients who received treatment in total with the box, at 24 hours:

- 10 (9%) patients were admitted to Critical Care, of which
- 1 (1%) patient died
- 104 (91%) remained on the ward and improved.

Use of the box by ward nursing staff

During the trial, ward staff rather than the CCOT initiated treatment using the sepsis box on 28 (25%) occasions and of these 1 patient was transferred to critical care with a NEWS of 12, and survived. Of these 28 patients treated:

- 1 patient had a NEWS of 12
- 2 patients had a NEWS of 11; and
- 25 patients had a NEWS of 9.

Discussion

The trial showed that initiation of the Sepsis 6 care bundle through use of the single-use Sepsis Box was linked to a significant drop in average NEWS at 24 hours, and with significantly fewer patients being referred to critical care than would normally be expected with such high NEWS scores.

The 25% of patients whose treatment was initiated by ward nursing staff were all very sick with a NEWS of 9 or greater, which would ordinarily be associated with an admission to critical care. Only one of these patients was admitted to critical care and survived.

As the trial was not randomised, compared to a control group, and had a small sample size, it is not possible to infer whether the

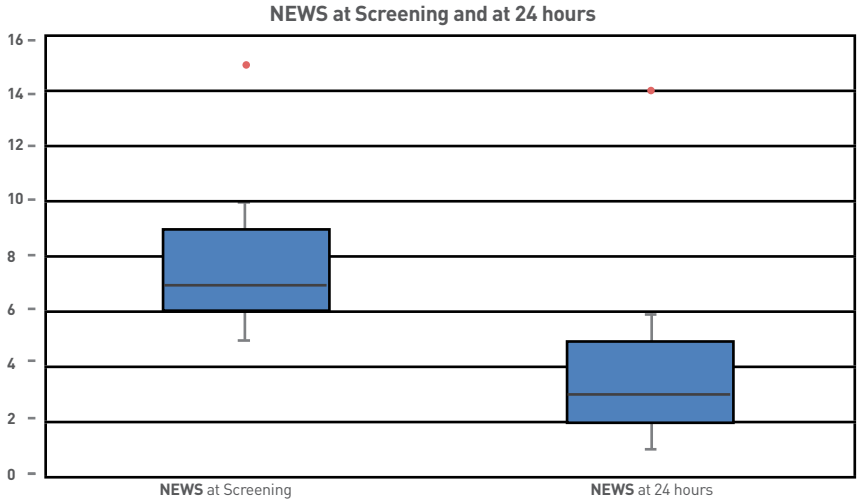

Figure 2. National Early Warning Score pre- and post- use of sepsis box (n=114)

Note: the horizontal line shows the Median rather than the Mean

positive outcomes are directly attributable to the unique features of the single use sepsis box, or are simply associated with the utilisation of any tool that drives the delivery of sepsis treatment in the clinical area.

If the latter then it is possible that the use of a bag, box or trolley influences a number of factors including reliability, error proofing, decision support and 'nudging' behavioural change.

Reliability

Reliability of healthcare delivery is poor. McGlynn et al. (2003) found the 'defect rate' in the delivery of healthcare to be 45% whilst Burnett et al. (2012) demonstrated reliability of care delivery at 80-90%, noting that these rates would not be tolerated by any other industry.

In promoting the idea of 'Safety 2' Hollnagel et al (2015) state that:

> *"Safety management should .... move from ensuring that 'as few things as possible go wrong' to ensuring that 'as many things as possible go right'"*

In seeking to ensure that as many things as possible do go right, in recent years clinicians have sought to learn lessons from other 'safety critical' high-reliability organisations (HROs) (Weick and Sutcliffe 2007; Health Foundation 2011).

An important lesson is how to mitigate for human error, by utilising a range of human factors principles, including 'error proofing' the system. Error proofing, or Poka Yoke as developed by the Toyota Production System, is intended to make it more difficult and to require more effort to do the 'wrong' thing and easier to do the correct action.

The sepsis box, containing all required items and instructions to perform the task, fulfils these criteria well. However, we should also be aware of the dangers of confirmation bias and potential for inappropriate overtreatment with unnecessary antibiotics in patients who do not have sepsis.

> **"the use of a piece of equipment to focus delivery of sepsis treatment can have positive outcomes for patients"**

Decision support

The first consensus statement on medical emergency teams (METs) (Devita et al. 2006) identifies the afferent and efferent arms of the rapid response system. The afferent part consists of the recognition of acute deterioration and a trigger to action whilst the efferent part consists of the response, usually by a team or individual with critical care expertise.

This binary approach continues to be used to describe the rapid response system and is undoubtedly useful. However, it is possible that it may be too simple a model to use when describing the actions around the treatment of an acutely, although not critically ill person, such as some with sepsis.

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report *Time to Intervene* (2012) identifies system failures not only in the recognition and response to the sick patient but also in the escalation process of their care. The UK Department of Health publication *Competencies for Recognising and Responding to Acutely Ill Patients in Hospital* (2009) identifies six possible roles in the recognition, escalation and response process, only the last of which necessitates the possession of critical care skills on the part of the responder.

The recent publication of a competency framework for caring for Level 1 patients (National Outreach Forum and Critical Care Networks 2018) is an acknowledgement of the fact that the hospital does not contain only the relatively well and those in need of a critical care response but that the landscape of patient acuity is more nuanced.

In short, it is apparent that there is a considerable amount of decision-making taking place between the points of recognition and response to sepsis and that this process involves achieving reliable communication of a shared mental model and establishing situational awareness amongst teams of nursing and medical staff in the acute setting.

It was evident during the study that the use of the sepsis box, alongside a standardised care bundle and screening tool, enhanced decision-making and promoted escalation of care to appropriate levels. This can be seen from the large number of patients with a NEWS that would normally indicate an ICU admission, remaining on the ward with a lower NEWS at 24 hours.

Behavioural change

The Health Foundation paper *Behavioural Insights in Healthcare* (Perry et al. 2015) identifies the provision of prompts and cues as well as using default options such as care bundles, as important tools in delivering behaviour change. The Behavioural Insights team (BIT) (Service et al. 2014) identify the acronym EAST™ (**E**asy **A**ttractive, **S**ocial and **T**imely) as descriptive

of successful behavioural change. The use of a focused prompt such as the sepsis box or trolley within the context of a rapid response system satisfies the requirements for an easy, attractive, social and timely approach to behaviour change.

Conclusion

Whilst limited in both sample size and evaluative rigour this study does, nevertheless, appear to indicate that the use of a piece of equipment to focus delivery of sepsis treatment can have positive outcomes for patients for a number of reasons. These may include design, effect on improving reliability, error proofing of the system, supporting decision-making in the sub-critical patient and in nudging a change in clinical behaviour.

Since the completion of the sepsis box study, the decision has been made by the commercial company on economic grounds, to cease production. Whilst this is disappointing it is nevertheless worth noting that a by-product of the trial and the interest shown in it is that all hospitals in Wales now aspire to situate a sepsis bag, box or trolley in all clinical areas. ■

Acknowledgements

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Conflict of interest

Chris Hancock declares that he has no conflict of interest. Andrew Hermon declares that he has no conflict of interest.

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Humanizing the ICU experience with enhanced communication

Avicenne ICU's initiative

Decisions to limit therapy (DTLT) are routine for ICU physicians. Although breaking bad news is one of the most difficult tasks clinicians face, ongoing communication is even more crucial as families (not necessary following a legal or genetic definition) of critically ill patients have heightened communication needs. Supporting families during the process of shared decision-making from the pursuit of cure/recovery to the pursuit of comfort/freedom of pain is a key concern for our ICU. Communication, including announcements, but also listening to families requires time and training. As few physicians had received formal training in how to deliver bad news, Avicenne ICU, with the help of a newly appointed psychologist, has developed specific training.

The early years of critical care medicine were defined by remarkable diagnosis and innovation, but were also associated with substantial suffering for patients and families, who were kept out of the units with strict visiting policies. Professionals expressed major concerns that clinical care might be impeded and that family members might become too emotional and out of control, exacerbated by a lack of availability of nurses to assist them. Communication was not a priority at that time, as physicians and nurses were focusing on technical skills (remember that in the 1940s, polio patients were ventilated by hand!)

Meanwhile, ICUs still remain synonymous with hope. "Resuscitation" as a word feeds immortality fantasies and sometimes leads families to request unreasonable CPR or invasive organ support for their loved ones.

For some years, the presence of family members has been discussed. There is an increasing recognition of their important role in the ICU, and high family-centred care should now be considered a basic skill for ICU clinicians. Recommendations include a more open visiting policy, and family conferences to promote ongoing communication and trust between family members and clinicians and thus lower the risks of anxiety, depression, and post-traumatic stress symptoms.

Intensive care is the ultimate symbol of state-of-the-art medicine. Despite efforts and innovation, death remains an outcome for 1 patient out of 4. About half of the deaths occur after a decision to limit or withdraw life-sustaining treatment.

Being ethical is at the centre of all discussions, and in France decisions are also regulated by law (Claeys-Leonetti law, February 2016). Withdrawing life support is a shared decision-making process that highlights the switch from a curative strategy to palliative care.

Withdrawing life support in ICUs may sound paradoxical for clinicians who traditionally have seen their goals as curing disease and restoring health and function. These goals must expand, when necessary, to also include assuring patients of a "good death."

When the decision is made, the announcement is a critical time for all actors

The announcement of a decision to limit therapy crystallises communication issues and puts a strain on each protagonist's coping mechanism:

- Weakened families go through emotional roller coasters because of anticipating the separation. Denial, *psychic sideration* (freeze response) are frequently observed.
- Breaking bad news is one of the most difficult tasks that physicians face. They sometimes feel a sense of failure in their mission, prompting them to use various coping methods such as avoidance, distancing or intellectualisation, keeping their distance to block their own feelings.

Between distressed physicians and confused families, the whole tragic situation can become a source of conflict, especially with a lack of or inadequate communication.

When DTLT are made, technical skills become less essential, but there is a risk of losing sight of the humanistic skills of medicine. It becomes even more important to stay with the patient, and to enhance communication with relatives. Listening and explaining are keys to alleviate their anxiety and help them enter the mourning phase.

Enhance communication to improve relationships: our programme

The appointment of a new psychologist in our ICU has been an occasion to step back and focus even more on high family-centred care with the objective of humanizing the ICU experience for all.

We noticed that communication could be improved with benefits both for families and doctors. Taking into account that few physicians had received formal training on this matter,

despite its crucial role today, we decided to develop our own training sessions focusing on breaking bad news.

The programme has been developed jointly by a doctor (Guillaume Van der Meersch) and the psychologist (Anne Rocher) with real cases. All medical residents and students who work in our unit attend a training session. The objective is to raise awareness and understanding of psychological ways of coping, and also to experiment in a secure and benevolent environment.

There is no good way of breaking bad news, but some can be less devastating than others. We talk about feeling and showing empathy, using the right words when appropriate and limiting jargon. We insist on the importance of body language and on making eye contact, and overall we focus on opening up to their own feelings, to also be open to families' feelings. We also take time to discuss how some situations impact our young doctors. Giving them the opportunity to experiment, to share and discuss these subjects is greatly appreciated. We also have noticed that families remain satisfied with the care they receive even once a decision to withdraw life support has been made.

Showing empathy, actively listening, learning how to demonstrate compassion, while delivering accurate and consistent messages helps to develop positive interactions and contributes to improving family-centred care.

Studies in different ICUs have shown that improving communication has a significant impact on lowering what has been termed "post-intensive care syndrome family" PICS-F (see aftertheicu.org/what-is-fics), reducing anxiety, depression and post-traumatic stress symptoms (Scheunemann et al. 2011; Gerritsen et al. 2017).

Although it is endless work, the "hospitality label" of our unit will ultimately highlight the human and highly emotional work, realised in the shadows every day by our physicians, care assistants and nurses who address the needs of families with bereavement counselling.

Psychologist in intensive care

As a non-medical third party, the psychologist can help to foster another type of speech, around patients. He/she can be in turn a partner of the announcement, a facilitator, an interpreter between different psychic realities, and even sometimes a mediator.

In the ICU, the psychologist is a bridge between worlds, his/her role is to facilitate the work of all actors and help each one find his/her role when facing end of life.

Taking care of the soul as we take care of the body requires taking into account the psychological and relational dimension as well as the medical technique. Speech and oxygen are both essential to life. ■

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Implementing ECCO$_2$R and vv-ECMO in non-academic centres

Shares experiences of implementing extracorporeal life support in a non-academic hospital.

Acute respiratory distress syndrome (ARDS) is a life-threatening disorder characterised by severe impairment of gas exchange. The most common causes are pneumonia, sepsis and acute pancreatitis. It is accurately defined in the Berlin definitions (ARDS Definition Task Force 2012). Progression to ARDS is associated with an increased risk of in-hospital mortality (46%) (Bellani et al. 2016). Despite substantial progress in understanding mechanisms of ARDS (Blondonnet et al. 2016), there has been little advancement in developing effective treatments. To date, causal therapy means treatment of the underlying decompensating factors causing ARDS. Additionally, so called "lung-protective" mechanical ventilation can reduce mortality in cases of severe ARDS (Acute Respiratory Distress Syndrome Network 2000).

Only two interventions have been shown to increase survival in ARDS patients (Tonelli et al. 2014): lung protective ventilation with low tidal volume (Acute Respiratory Distress Syndrome Network 2000) and prone positioning (Guérin et al. 2013). Each intensive care unit should be able to treat lung protectively like this. In life-threatening cases where conventional lung-protective ventilation fails, extracorporeal membrane oxygenation (ECMO) can represent a life-saving alternative to treat ARDS and refractory hypoxaemia, to stabilise gas exchange and serve as a temporary replacement of pulmonary function and bridge to recovery. Recent evidence from a large multicentric, randomised trial suggested a potential positive effect of the use of veno-venous (VV) ECMO in refractory ARDS in terms of mortality and complications (Peek et al. 2009). In the past, extracorporeal lung support of ARDS was the domain only of large centres, because the need for personnel and technical resources was immense. The newest improvements for VV-ECMO applications provide the full spectrum of extrapulmonary lung support, from efficient carbon dioxide removal to complete oxygenation. The development of the acquired techniques and hardware meanwhile allows easier handling than before. Nevertheless, these techniques should only be used in clearly selected patients e.g. following the Extracorporeal Life Support Organization (ELSO) guidelines (Brogan et al. 2017).

Implementing ECCO$_2$R/vv-ECMO in non-academic centres therefore is quite possible if one takes care of the depending expertise: which patients are we able to handle, which therapy is realisable and most important: which adverse events are we able to cope with? We started to think about this treatment at our clinic, as in the past there had been sporadic difficulties to transmit ARDS patients to other centres because they had not the capacity to treat our patients in the required moment.

There are several personal and structural specifications needed: qualified intensivists and nurses in 24-hour shifts, surgical, radiologic and medical support if needed 24/7, including echocardiography, bronchoscopy and CT scans. One of our most important aims in implementing this therapy was teaching the staff and team building. In the last 5 years we treated 63 patients with ECCO$_2$R/vv-ECMO, selected from our ARDS patients. In 2015 we joined the German ARDS Network group and last year ELSO. Since that time we are following ELSO guidelines in indicating this therapy. In the ECMO-implementing phase within the first two years company support came in house for each patient to teach staff and to stay for trouble-shooting. Meanwhile we need about two hours from clinical decision to start the therapy. In the phase of inserting the catheters and installing the machine, the ECMO team is exclusively responsible for these actions. Patients with VV-ECMO require one nurse per patient all the time.

As shown in the literature, in centres with 5 or less annual treatments mortality increases (Barbaro et al. 2015). Position papers therefore define required structures (Combes et al. 2014). In our hospital we reach an overall survival rate from > 50% in our ECMO patients, treating 12 patients/year. This is quite similar to ELSO data (Brogan et al. 2016) and the ALIVE study data (Brun-Buisson et al. 2004). Guidelines from the German Society of Anaesthesiology and Intensive Care (DGAI) postulate not less than 20 treatments per year (Adamzik et al. 2017).

Conclusion

Summing up, the more patients you treat, the more effect for your patients you gain. Centres that aim to treat with VV-ECMO must be able to treat the whole patient with all the problems and difficulties alongside. That requires clear decisions and pathways in indication and contraindication for this treatment as well as benchmarking and peer review. ■

Conflict of interest

Klaus Kogelmann has received lecture honorary and travel fees from Cytosorbents Corp, Xenios AG and Sedana medicalo

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/o2e

Highlights from the I-I-I Blog (I expert, I question, I answer)

Have you got something to say?

A selection from the ICU Management & Practice I-I-I blog. Have you got something to say?
Visit https://healthmanagement.org/c/icu/list/blog or contact editorial@icu-management.org

Jean Baptiste Lascarrou

Medical Intensive Care Unit, Nantes University Hospital, France
@jblascarrou

Epinephrine for out-of-hospital cardiac arrest

"Epinephrine (or adrenaline for EU physicians) has alpha-adrenergic action which leads to increased coronary blood flow but also beta-adrenergic action that can lead to the recurrence of VF/VT and can also impair cerebral microvascular blood flow. Additionally, recent data from randomised controlled trials on cardiogenic shock) or meta-analysis highlight poor outcome associated with epinephrine use. In this context, clinical trial of drug use with only "alpha-adrenergic" action such as norepinephrine deserves attention."

See more at: https://iii.hm/ns5

Linda Kennemar

Critical Care Nurse - Nyköping Hospital, Sweden
@katrobot75

How ICU diaries can help patients and families

"The importance of the diaries is demonstrated when patients have vivid memories and the diaries are able to provide explanations. For example, a patient remembers his throat being cut with a knife; the diary tells the patient he had a central venous catheter put in and we can then explain the procedure to him. Patients have such wide-ranging comments. It is often a relief for them to tell us stories their relatives don't believe and sometimes we can help them find some kind of reality in the story or just reassure them that it can be like that after ICU."

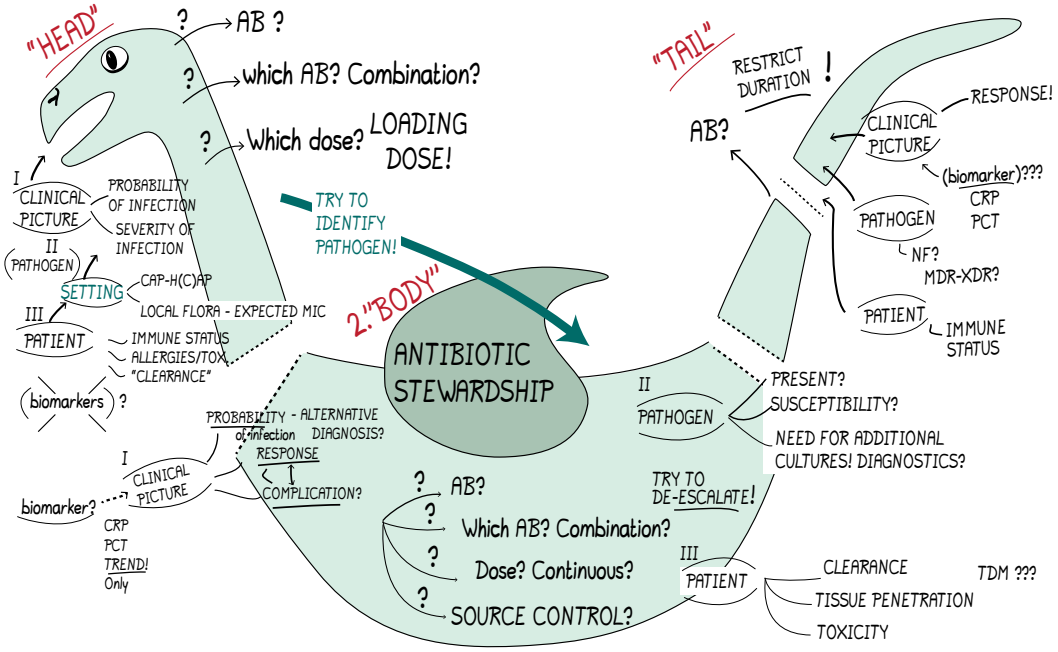
See more at: https://iii.hm/ns6

Pieter Depuydt

Head of Clinic - Department of Intensive Care, Ghent University Hospital, Belgium

Antibiotic decisions in the ICU: a dragon's tale

See more at: https://iii.hm/ns7



Improving access to safe anaesthesia

Interview with Jannicke Mellin-Olsen, President, World Federation of Societies of Anaesthesiologists

Jannicke Mellin-Olsen, MD, DPH is Consultant Anaesthesiologist at the Department of Anaesthesia, Intensive Care and Emergency Medicine, Bærum Hospital, Norway. She is President of the World Federation of Societies of Anaesthesiologists, and serves as a member of the Patient Safety and Quality Committee of the European Society of Anaesthesiology. Dr. Mellin-Olsen is on the Patient Safety Movement Foundation's Board of Directors and is the Foundation's Regional Network Chair. Dr. Mellin-Olsen served in the UN Peace Keeping Forces in Lebanon and for the Red Cross in Pakistan and Serbia, and for 10 years was the medical director for Europe, Middle East, and Africa for MedAire, Inc., which provides remote medical services to patients in the air and at sea. She is past president of the Norwegian Society in Anaesthesiology and past President of the European Board of Anaesthesiology. Her Twitter handle is @jmellinolsen.

Eight years on from the Helsinki Declaration on Patient Safety in Anaesthesiology what would the report card say?

It has been a surprise how much it has spread beyond Europe, illustrating that the anaesthesiology world and our partners see the need to improve safety for our patients. The map says it all (**https://iii.hm/noi**). But a signature does not mean improvement per se, it must be followed up by committed actions.

What are your priorities as President of the World Federation of Societies of Anaesthesiologists (WFSA)?

The WFSA mission is to unite anaesthesiologists around the world to improve patient care and access to safe anaesthesia and perioperative medicine. I have noticed that in high-, middle- and low-income countries, we are driven by the same goal—we want to help our patients. Five out of seven billion people in this world do not have access to safe, timely and affordable anaesthesia and surgery. This must be changed, and we anaesthesiologists cannot expect anyone other than ourselves to drive that change. We must lead by creating awareness of the situation, advocate, set standards and educate.

The WFSA's global workforce survey highlighted the lack of anaesthesia in many parts of the world:

How can this gap be closed? It must be a combination of workforce expansion, education, investing in facilities and equipment, including anaesthesia drugs, and improving the living and working situation to reduce emigration and more. We need to help policy makers and decision makers understand that they must provide sustainable plans for scale-up.

How is the WFSA working on the interim goal of at least 5 specialist physician anaesthesia providers per 100K population? The Lancet Commission on Global Surgery (**thelancet.com/commissions/global-surgery**) estimated that there should be at least 20 surgeons + obstetricians + anaesthesiologists per 100K. We estimated that of those, a bare minimum of 5 must be anaesthesiologists to lead and educate in addition to some direct patient care. The WFSA is working on many fronts. We are now developing a Training Framework, we do training ourselves—for instance the SAFE Courses and all our training centres, we have developed the WHO-WFSA Standards for Safe Anaesthesia, we work with governments on National Surgical, Obstetric and Anaesthesia Plans and more.

What work is being undertaken to define and map non-physician anaesthesia providers as well as infrastructure and

equipment? Non-physician anaesthesia providers are also counted in our Workforce Study, which will be repeated during the coming two years.

What's behind the WFSA campaign #KetamineisMedicine?

Where there are limited resources, like when there is no oxygen, no electricity or no equipment and limited training, ketamine is often the only available anaesthetic. China has called for international scheduling, as Chinese ketamine has been used as a recreational drug in neighbouring countries. They have been supported by some other countries where there is illicit use of ketamine. The morphine experience taught us that when medicines are scheduled, the medical usage is dramatically reduced, although countries are supposed to ensure that they are available for medical purposes. An example is when India enacted the Narcotic Drugs and Psychotropic Substances Act in November 1985 (Mohan and Bansal 2005). So many bureaucratic restrictions were put in place that doctors stopped taking morphine from the pharmacies, who in turn, stopped stocking it, and the manufacturers stopped producing a medicine nobody bought. The use of medicinal morphine dropped by 97%. There is no reason to believe that it would be different for ketamine, which would be a disaster for patients.

The WFSA raised concerns about the recommendation on FiO_2 in the World Health Organization guidelines to prevent surgical site infections—has this been amended?

Our concerns were twofold—one is that even in high-income settings, it is very difficult to maintain a level of FiO_2 0,8 during the whole perioperative period, so it does not make sense to recommend it. The other is of course, the effect of a high FiO_2 on lungs with atelectasis and other problems. The WHO took our input seriously but have not been willing to change the recommendation yet. However, since these discussions started, one of the papers by Schietroma has been retracted, so they have now excluded all his papers previously included in their reviews, and the strength of evidence changed. Therefore, they have decided to reconvene the Guidelines Development Group and expand it with more anaesthesiologists. We are also now involved in a Dutch study looking into the actual practice of perioperative FiO_2 administration throughout the world.

What is holding back gender equity in anaesthesiology and how can this be improved?

The same factors as in other fields of medicine and in society in general. It is a multifaceted problem: Medicine should be gender balanced, to meet the patient mass which is 50/50. Yet, medicine as a profession is being feminised. Hence, we need to investigate factors preventing men to apply to medical school. But the increased female workforce is not reflected in leadership positions and academics. The reasons are multiple, so the measures must be multiple: as it is now, there is a positive discrimination in the way that people have a tendency to select and appoint people who resemble themselves. When the "selectors" are white, middle-aged men, they tend to recruit other white middle-aged men. Therefore, there must be a mechanism to actively identify people that "are different" but not sacrificing quality. Quotas have also been used with success in my country, but it is controversial. Role models and good mentors (not necessarily of your own gender) are also important.

> "five out of seven billion people in this world do not have access to safe, timely and affordable anaesthesia and surgery"

What is meant by critical emergency medicine (Böttiger et al. 2018)? What are the basic principles of CREM?

There has been and is some controversy regarding "emergency medicine" in Europe and beyond. Anaesthesiologists view emergency medicine as one of the pillars in our speciality, and the European Board of Anaesthesiology and the European Society of Anaesthesiology have not been supportive of a basic speciality in emergency medicine. Yet, "our" emergency medicine represents only the critical part—ten percent of what the speciality claims, while 90% of their speciality is totally something else. We argue that those most critical patients are better served by a team approach where we contribute what we are good at, supporting airways and circulation in those critical patients.

Who should manage the airway in an emergency outside the hospital and inside?

Basic airway management—jaw thrust and mask and bag ventilation should be a basic competence of all health workers. Advanced airway management should not be defined by designation, but by competence. Health systems are different, so one cannot transplant one system to another. But in times where for instance laryngeal mask is replacing endotracheal intubation, it should not be spread on too many professions as it will be difficult to obtain and maintain that competence. Therefore, as a rule inside the hospital it should be that anaesthesia personnel are in charge. Outside the hospital, the trend is that intubation is being replaced by subglottic airways, and that is probably a good trend. ■

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European Society of Anaesthesiology (2010) Helsinki Declaration. Available from esahq.org/patient-safety/patient-safety/helsinki-declaration/full-declaration

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AGENDA

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

OCTOBER

30-3 Nov EAPS 2018: 7th Congress of the European Academy of Paediatric Societies
Paris, France
https://iii.hm/o1c

NOVEMBER

1-3 7th Annual Johns Hopkins Critical Care Rehabilitation Conference
Baltimore, USA
https://iii.hm/o1d

6-9 Critical Care Canada Forum 2018
Toronto, Canada
https://iii.hm/o1e

7-9 10th Euro Neuro Brussels 2018
Brussels, Belgium
https://iii.hm/o1f

9-10 ESA Focus Meeting on Perioperative Medicine 2018
https://iii.hm/o1g

9-11 6th European Conference on Weaning and Rehabilitation
Leuven, Belgium
https://iii.hm/o1h

13-15 Echocardiography for Hemodynamic Monitoring 2018
Brussels, Belgium
https://iii.hm/o1i

23 7th International Fluid Academy Day 2018 - IFAD
Amsterdam, The Netherlands
https://iii.hm/o1j

DECEMBER

4-6 24th Postgraduate Refresher Course on Cardiovascular and Respiratory Physiology Applied to ICM,
Brussels, Belgium
https://iii.hm/o1k

4-7 5th European Airway Management Society Congress
Catania, Italy
https://iii.hm/o1l

16-19 Update on Cardiac Arrest
Rome, Italy
https://iii.hm/o1m

JANUARY

7-11 Blood Diseases in the ICU: Advanced Training
Paris, France
https://iii.hm/o1n

15-17 ICU Leadership 2019
Brussels, Belgium
https://iii.hm/o1p

30-31 CRITICARE 2019: 25th Annual Conference of Indian Society of Critical Care Medicine
Mumbai, India
https://iii.hm/o1q

FEBRUARY

4-7 Canadian Critical Care Conference 2019
Whistler, Canada
https://iii.hm/o1r

7-8 24th International Symposium on Infections in the Critically Ill Patient
Seville, Spain
https://iii.hm/o1s

17-20 SCCM 2019-48th Annual Meeting of the Society of Critical Care Medicine, San Diego, USA
https://iii.hm/o1t

21-24 15th WINFOCUS World Congress on Ultrasound in Emergency & Critical Care
Dubai, UAE
https://iii.hm/o1u

MARCH

19-22 ISICEM 2019-39th International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium
https://iii.hm/o1v

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Monday 22nd of October

Tailoring the hemodynamic monitoring according to clinical needs

12:30 – 14:00 / Room Geneva

Chairmen
Thomas Scheeren (Groningen, The Netherlands)
and **Daniel Reuter** (Rostock, Germany)

Jean-Louis Vincent (Brussels, Belgium)
Clinical challenge in the ICU – identification and monitoring

Bernd Saugel (Hamburg, Germany)
When do we need hemodynamic monitoring?

Frédéric Michard (Lausanne, Switzerland)
Fluid responsiveness – measurement technology in ED, OR and ICU

Marit Habicher (Giessen, Germany)
Successful implementation of optimized fluid management

Tuesday 23rd of October

Future practice in hemodynamic monitoring

12:30 – 14:00 / Room Geneva

Chairmen
Maurizio Cecconi (London, UK) and
Ignacio Monge Garcia (Jerez, Spain)

Bernd Saugel (Hamburg, Germany)
Clinical impact of hypotension

Bart Geerts (Amsterdam, The Netherlands)
Big Data in Clinical Practice

Michael Sander (Giessen, Germany)
Predicting hypotension – from reactive to proactive clinical decision

Frédéric Michard (Lausanne, Switzerland)
Predictive analytics – beyond the buzz

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