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THE OFFICIAL MANAGEMENT AND PRACTICE JOURNAL

VOLUME 15 - **ISSUE** 3 - **AUTUMN** 2015

The Brain

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Michael R. Pinsky, MD, CM, Dr hc, FCCP, FCCM

Professor of Critical Care Medicine, Bioengineering, Anesthesiology, Cardiovascular Diseases, and Clinical & Translational Sciences
Vice Chair for Academic Affairs UPMC, Pittsburgh, Pennsylvania

The Role of Non-invasive Assessment of Fluid Responsiveness in the OR and ICU

Jean-Louis Teboul, MD, PhD

Professor of Anaesthesia and Critical Care Medicine
Hospital CHU Bicêtre, Department of Intensive Care
University Hospital and School of Medicine Paris-Sud
Le Kremlin Bicêtre, Paris, France

New Paradigms in Patient Blood Management

Aryeh Shander, MD, FCCM, FCCP

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

Non-invasive Monitoring of Oxygen Delivery: New Frontiers

Azriel Perel, MD

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THE BRAIN

Treatment of neurological illnesses and complications in the intensive care unit remains a challenge. And as intensivists we are aware of the risks of cognitive impairment for many ICU patients. For our cover story this issue we address practical brain matters.

Nino Stochetti explains how to choose fluids for brain injured patients to achieve the goals of preserving cerebral perfusion, controlling brain volume and assuring appropriate substrate delivery. Next, Geert Meyfroidt and Romain Sonneville consider whether "less is more" in sedation in acute brain injury, looking at current sedation practices in the neuro-ICU, and what sedative to choose. Then Jens Schröder, Jörg Glahn and Rainer Dziewas discuss ICU-related dysphagia. They present the diversity of pathogenetic factors, evaluate existing diagnostic procedures and give pragmatic recommendations for the diagnostic approach as well as for the further nutritional management of ICU patients.

Continuing our series on Infections, Joseph David Cooper, Shravan Kethireddy and Anand Kumar provide a primer for infections in the immunosuppressed and immunocompromised patient. Patients with impaired immune function are a growing group, and their review focuses on the biological basis for immune dysfunction and clinical assessment.

In the Matrix section, Jan Wernerman and Olav Rooyackers provide an update on nutrition monitoring. They note that while monitoring nutrition is not complicated or difficult, it is more problematic to monitor nutritional risk and to define the purpose or target for nutrition. Next, Barbara Presello, Francesca Di Muzio, Glenn Eastwood, and Rinaldo Bellomo argue the case for liberal glycaemic management. They note that the evidence suggests that glycaemic management algorithms should be tailored differently for diabetic and non-diabetic patients and that "permissive moderate hyperglycaemia" may be justified in diabetic patients. Fernando Suarez Sipman and Gerardo Tusman describe heart-lung interactions from the lung's perspective. They contend that implementing a protective ventilatory strategy extended to the lung, the pulmonary circulation and the right ventricle should constitute an early target during mechanical ventilation in ARDS patients. Finally, Manu Malbrain, Yannick Peeters and Robert Wise discuss current evidence on the available resuscitation fluids as well as the endpoints that can be used to guide fluid resuscitation in burns.

Benchmarking in critical care has been around for 20 years. In our Management section Matti Reinikainen and Hans Flaaten outline the pitfalls of benchmarking and concentrate on the challenges of comparing severity of illness-adjusted mortality figures. Our interview is with Hannah Wunsch, who considers the whys and wherefores of intensive care systems research. Finally, we wrap up this issue with an interview with Claudio Martin, President of the Canadian Critical Care Society for our Country Focus on Canada.

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

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BOOK REVIEW

There are not many good books on this topic, and the present one includes contributions from North American and Australian experts in the field. The book has three main sections: organisation, improvement and integration, and a shorter fourth section on global and future perspectives.

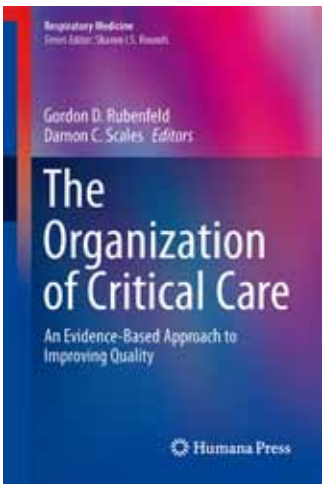
The list of topics is quite comprehensive, from ICU practitioners to computers, from quality to teamwork, from rationing to rapid response teams. Some topics are somewhat weird, like the "chronically critically ill", a certainly challenging but awkward concept. The chapters are usually well written, quite focused, but sometimes a bit too short, especially towards the end of the book, with only a few pages on disaster planning.

I was surprised to see the lack of participation from outside North America and Australia (except for a single author from the UK). The chapter on international perspectives is quite incomplete, as it does not cite important international studies; the aspects on critical care in low resource settings could have involved leaders from outside North America.

Potential readership is an uneasy question. Probably not the average ICU practitioner, nor specialists in the field, but more those who have an interest in hospital organisation and healthcare organisation, and do not know much about critical care medicine. In just a few hours, one can grasp a number of important issues related to the specialty.

The organization of critical care: an evidence-based approach to improving quality. DC Scales, GD Rubenfeld, eds. Humana Press. ISBN 978-1-4939-0810-3 (hardcover); ISBN 978-1-4939-0811-0 (ebook).

Jean-Louis Vincent



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ICU Management

is the Official Management and Practice Journal of the International Symposium on Intensive Care and Emergency Medicine and was previously published as Hospital Critical Care.

FLUID CHOICES IN BRAIN INJURY

Goals of fluid therapy in brain injury are euvolaemia and normal plasma osmolarity, with glucose in the usual range. The appropriate level of haemoglobin has still to be clarified.

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Fluid management for acute brain damage has changed profoundly in the last decades. In the recent past brain oedema has been identified at autopsies as an overwhelming cause of raised intracranial pressure (ICP) and death after brain injury. In order to reduce the brain water content, dehydration, and even drastic dehydration, with 250 ml/day total, has been proposed for ICP treatment in severe brain trauma (Benabid et al. 1980). At the other extreme a generous fluid infusion, leading to hypervolaemia, was recommended to counteract vasospasm after subarachnoid haemorrhage (SAH) (Kassel et al. 1982).

These extreme approaches were based on incomplete understanding of water dynamics in the brain and cerebral blood flow (CBF) autoregulation.

Water moves from the intravascular to the extra- and intra-cellular space along osmotic gradients, while sodium, with an intact blood brain barrier (BBB), does not.

This has two consequences: any subject with a normal plasma osmolarity will not reduce his brain water content as a consequence of dehydration. Moreover, osmolar gradients can move water from the tissue toward the plasma compartment: therefore osmotic agents have been infused to reduce brain oedema (Qureshi and Suarez 2000).

If pressure autoregulation is preserved, CBF doesn't depend on volaemia or cardiac output, but on cerebral perfusion pressure (CPP) and cerebrovascular resistances. Hypervolaemia, under these conditions, will not increase CBF nor counteract vasospasm.

Goals of Fluid Therapy in Acute Brain Injury

The choice of fluids for severe patients with acute brain injury should respect three priorities:

1. To preserve cerebral perfusion;
2. To control brain volume; and
3. To assure appropriate substrate delivery.

Maintaining Cerebral Perfusion: Haemoglobin and Volaemia

Oxygen content and delivery are essential. The appropriate level of haemoglobin (Hb) for patients at risk of cerebral ischaemia has been debated and is still not firmly established. There are arguments in favour and against liberal transfusion policies (Utter et al. 2011). A recent literature review found insufficient evidence to confirm or refute a difference in effect between lower and higher Hb groups in neurocritically ill patients (Desjardins et al. 2012). A randomised study in 200 traumatic brain injury (TBI) patients (Robertson et al. 2014) has not demonstrated an improved neurological outcome at 6 months maintaining haemoglobin concentration of greater than 10g/dL, but the design of the study and the low patient numbers reduce the external validity of the study.

The more recent trend, which suggests a threshold as low as 7g of Hb (Hébert and Carson 2014), may be risky if microcirculation doesn't guarantee adequate flow to the injured brain. Higher thresholds are currently suggested by guidelines (Diringer et al. 2011; Retter et al. 2013).

Initial enthusiasm for volume expansion and hypervolaemia to prevent ischaemic neurologic deficits after SAH (Kassell et al. 1982) has been blunted by more rigorous examination. While avoidance of hypovolaemia and hypotension has a strong rationale, benefits from hypervolaemia are not proven, according to a systematic literature review (Treggiari et al. 2003). When hypervolaemia has been tested in comparison with induced arterial hypertension in the treatment of ischaemia after SAH, scarce benefits were demonstrated in restoring tissue oxygenation, at the expense of increased systemic complications (Raabe et al. 2005). A more recent study on 10 SAH patients demonstrated a modest CBF improvement following hypervolaemia, unfortunately associated with worse brain tissue oxygenation (Muench et al. 2007).

Volaemia should be normal, and there are no data supporting colloids rather than crystalloids. Hypotension in the first phase after trauma is associated with higher mortality and unfavourable outcome, so that appropriate fluid infusion, with the target of normo-volaemia and normal arterial pressure, is mandatory. Prehospital management with intravenous hypertonic saline, compared with resuscitation with conventional fluids, has been tested in patients with severe TBI, who suffered hypotension in the early phase after injury. Hypertonic fluids did not improve long-term neurological outcome (Cooper et al. 2004).

> "Careful avoidance of hypo-osmolarity is key"

Albumin 4% has also been tested in the first 28 days after TBI. Its use, unfortunately, was associated with worse outcome compared to controls. One plausible explanation of this finding is that albumin was associated with a higher ICP level (Cooper et al. 2013). On the contrary, albumin is still often used in SAH patients, probably because volume expansion, even if of unproven benefit, remains popular (Suarez et al. 2014).

Controlling Intracellular Volume

Normal plasma osmolarity is essential for prevention of intracellular swelling. As mentioned, water moves from the extracellular space to the intracellular compartment when

an osmotic gradient is created, so that careful avoidance of hypo-osmolarity is key in neurointensive care. Hyponatraemia may worsen cerebral oedema and mass effect, leading to an ICP increase, with potential deleterious effect on outcome. Unfortunately hyponatraemia is frequent during the acute phase following TBI or aneurysmal SAH (Qureshi et al. 2002).

Ideally, the BBB should be intact, making the transit of large molecules into the brain tissue tightly controlled. Under these conditions, a predictable water movement is created, simply based on the osmotic gradients from the intravascular compartment to the brain tissue.

The reflection coefficient describes the selectivity of the BBB to a given molecule. Compounds with a coefficient of 1 are totally excluded by the BBB, while lower coefficients indicate an easier BBB crossing. Sodium chloride has a coefficient close to 1, while mannitol, with a higher molecular weight, has a coefficient of 0.9 (Qureshi and Suarez 2000).

Often, however, the BBB is damaged, as in case of brain contusion, which is associated with increased permeability and oedema. Water and proteins can enter the brain through areas of disrupted BBB, causing oedema (vasogenic oedema). If the BBB is damaged, the net flow of water and molecules from the intravascular compartment to the tissue becomes very complex. Since several molecules can pass the altered BBB and accumulate in the tissue, there is a significant risk of increasing brain tissue osmolarity, if osmotic compounds are infused. In this case a worsening of brain oedema becomes likely.

Studies on the BBB behaviour in the clinical setting are difficult, while this issue has been explored in experimental conditions. In a rodent model of closed brain injury, for instance, trauma was associated with a rapid BBB opening lasting only 30 minutes (Barzo et al. 1996). More recently, in a limited sample of TBI patients, BBB dysfunction (defined as a cerebrospinal fluid-plasma albumin quotient of ≥0.007) has been investigated. More than one-third of the patients showed signs of BBB alteration (Saw et al. 2014).

Water movements in response to osmotic gradients can, however, be used to withdraw water from the injured tissue, by using osmotically active molecules. If plasma osmolarity could be increased without affecting intracerebral concentration of osmoles, the brain water content will be reduced.

Historically, urea and glycerol have been used in order to control brain oedema and reduce ICP, but with relevant side effects. Mannitol has gained popularity for being more effective and associated with fewer complications. Its effects are not limited to brain dehydration, since mannitol might also have vascular effects, with an initial CBF increase and a subsequent vasoconstriction (Muizelaar et al. 1984).

Hypertonic saline solutions have been used for ICP control in the last 30 years. In animal models with focal injury and in several clinical studies hypertonic saline causes a prompt ICP reduction that is thought to be caused by a reduction in water content in areas of the brain with intact BBB (Dias et al. 2014; Torre-Healy et al. 2012; Kamel et al. 2011; Battistella and Wisner 1991).

Comparisons with mannitol suggest almost equal efficacy in reducing ICP, but there are conflicting data concerning the respective duration of action (Battison et al. 2005; Qureshi and Suarez 2000).

Providing Appropriate Substrate Delivery

The brain uses preferentially glucose for its energy metabolism and has very limited glycogen storage. Continuous glucose delivery is therefore mandatory. Glucose enters the brain through a mechanism of facilitated transport, and the brain extracellular concentration depends on the plasma concentration. The deleterious effects of acute and chronic hyper- and hypoglycaemia on the brain have been demonstrated, so that maintenance of normoglycaemia is desirable (Vespa 2008; Suh et al. 2007; Tomlinson and Gardiner 2008).

The possible benefits of tight glycaemic control, however, should be weighed against the risks of hypoglycaemia. Several studies have demonstrated (Nasraway 2007) glycaemic values below 40 mg/dL in various proportions: from 4% in high quality centres up to 18-19% in other institutions. Vespa and colleagues (2006) have shown that intensive insulin therapy reduces brain extracellular glucose concentrations without modifying the lactate/pyruvate ratio. Magnoni, moreover, has demonstrated that the interstitial levels of glucose are reduced, for the same systemic glucose concentration, in the metabolically injured brain (Magnoni et al. 2012). For all these reasons, great attention should be given to the avoidance of hypoglycaemia.

Conclusion

After acute brain damage choices in fluid therapy should aim at a normal systemic haemodynamic, in order to guarantee adequate CBF, while providing adequate oxygen and substrate (mainly glucose) content in the general circulation. Special attention to osmolarity is also necessary to prevent, or mitigate, brain oedema. ■

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COGNITIVE IMPAIRMENT AFTER CRITICAL ILLNESS

PREVENTION AND TREATMENT

Prof. Ignacio J. Previgliano
is Head of Intensive Care, Hospital General de Agudos J. A. Fernández, Buenos Aires, Argentina. He talked to *ICU Management* about his investigations into the use of neurotrophic factor preparation (NTF-prep) for cognitive impairment after critical illness.

Why did you decide to investigate NTF-prep?

Long-term cognitive impairment after critical illness (CIACI) was first described in 1999 (Hopkins 1999). In 1992 we noticed that in cardiac surgery with extracorporeal circulation patients there was a correlation between jugular bulb lactic acid and cognitive decline. We concluded that CIACI was a real dementia, not a post-traumatic stress disorder (Previgliano 2015). Pandharipande et al. revealed that impairment was independently associated with duration of delirium (Pandharipande et al. 2013). Analysing delirium pathophysiology under the physiologic mechanisms of brain cell death and survival, including the neurovascular unit (NVU) concept, led us to conclude that vascular ischaemia, necrosis and apoptotic mechanisms were involved or triggered in CIACI. Endogenous neurotrophic factors (ENTF), as brain-derived neurotrophic factor (BDNF), were found to be involved in almost all stages of development of neural circuits, with a key role in synaptic N-methyl-D-aspartate transmission activity, inflammation and apoptosis regulation. Natural neurotrophic factor preparation (NTF-prep; commercially available as Cerebrolysin®) acts like endogenous neurotrophic factors and showed clinical efficacy in Alzheimer's disease (AD), vascular dementia, ischaemic stroke and traumatic brain injury (TBI). We hypothesised that NTF-prep could play a neuroprotective role at delirium onset, or a neurotrophic or neurogenic one when CIACI was present.

How might NTF-prep be useful for prevention and treatment of CIACI?

NTF-prep was shown to stimulate angiogenesis, neurogenesis, remyelination, cell migration, suppression of apoptotic-like processes and recovery of functional NVU. These findings were translated into improved functional outcomes in various animal models. They were shown to act through sonic hedgehog and neurotrophic signal transduction pathways, which are part of the endogenous mechanisms of neuroprotection and neurorestoration. Our hypothesis is that due to this neuroprotective action NTF-prep could be effective in CIACI prevention. For this setting a 30 ml/day infusion for 10 days, as used for stroke, might prevent CIACI development.

Once CIACI is present the clinical picture resembles mild cognitive impairment or mild dementia. In dementia, NTF-prep has showed improvement over placebo in 12 randomised controlled studies. In a trial in Argentina on NTF-prep in 202 AD and mixed dementia patients, we found a 70% improvement. For CIACI treatment we think the regimen of 10 ml/day for 20 days repeated each three months, as used in dementia, could be suitable.

What might be the advantages of NTF-prep compared to the delirium care bundle?

The delirium care bundle includes sedation suspension, spontaneous ventilation assays, early mobility and sleep hygiene programmes (Barr et al. 2013). While it is associated with significant improvements, it is an example of how endogenous defence mechanisms can be triggered. Awakening patients augments cerebral blood flow and generates local NTF release, as does physical activity. The muscle must be seen as an endocrine system with endocrine, autocrine or paracrine effects. There is a clear relationship between levels of IL6 and BDNF, exercise and improved cognitive function. As BDNF is a large molecule it cannot pass through the NVU and blood brain barrier (BBB), so an endocrine and paracrine activation gear promotes BDNF release within the brain. NTF-prep is produced by an enzymatic breakdown of purified porcine brain proteins, and contains a complex mixture of <10 kDa peptides that was shown to stimulate neurotrophic signalling pathway as well as endogenous production of NTFs. Therefore, NTF-prep acts in a similar way to ENTF, but is able to cross the BBB. In this way it could be used in conjunction with the delirium care bundle to protect the brain.

What might be the potential risks of NTF-prep?

A review of NTF-prep safety in randomised clinical trials of dementia and stroke found no differences with the placebo (Thome and Doppler 2012). Adverse effects were generally mild and transient. Prescribing information warns about anaphylactic reactions in less than 10^{-100} of patients. NTF-prep appears to be safe when used in combination with recombinant tissue plasminogen activator or cholinesterase inhibitors such as donepezil or rivastigmine.

NTF-prep is already in use for TBI and stroke patients. What are the results? What is your own experience?

A randomised clinical trial in 1,070 patients with acute ischaemic stroke found no significant difference 90 days after stroke onset between patients receiving the NTF-prep or placebo (Heiss et al. 2012). A post-hoc analysis, however, showed a trend in favour of the NTF-prep in patients with a National Institutes of Health Stroke Score >12. The cumulative mortality at day 90 was significantly lower; 20.2% in the placebo group and 10.5% in the treatment group. The morbidity was lower in the treatment group with an improvement of 4.8 points versus 1.8 points for placebo. A consistent, across all clinical studies in acute brain injuries, is accelerated recovery pattern reflecting activation of consciousness, motor and cognitive functions. These clinical effects might be of relevance for supporting delirium care bundle. A recent trial investigated the cognitive effects of the NTF-prep in mild TBI patients. It found that the acute administration

of the NTF-prep resulted in the recovery of cognitive deterioration as assessed at 1 and 3 months post-injury (Chen et al. 2013).

Our experience, in 18 patients surviving severe TBI that developed post-traumatic dementia, treated with NTF-prep at the dementia dosage and quarterly cycles, showed significant improvement in memory, executive and motor function. Transcranial Doppler studies revealed significant improvements in cerebral blood flow velocities in both middle cerebral and basilar arteries, and in estimated cerebral perfusion pressure, with a decrease in pulsatility index reflecting a drop in cerebrovascular resistance.

What further research is needed?

Although NTF-prep is approved in many countries to treat dementia, stroke and TBI, and all these diseases have common pathways with CIACI, we still need to prove that our hypothesis on prevention is correct. A dedicated clinical development programme could provide the answer. ■

Abbreviations

BBB Blood brain barrier
BDNF Brain-derived neurotrophic factors
CIACI Cognitive impairment after critical illness
IL6 Interleukin-6
ENTF Endogenous neurotrophic factors
NTF-prep Neurotrophic factor preparation
NVU Neurovascular unit
TBI Traumatic brain injury

DISCLOSURE:

"Point-of-View" articles are part of the ICU Management Corporate Engagement Programme

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SEDATION IN ACUTE BRAIN INJURY

LESS IS MORE?

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Over the past decades, landmark interventional studies in general intensive care unit (ICU) patients have taught us that efforts to reduce the use of sedatives, by daily interruption (Kress et al. 2000; Girard et al. 2008), by not using sedatives as standard practice (Strøm et al. 2010), or by tapering sedatives to an awake but comfortable state (Mehta et al. 2012), lead to improvements in outcomes. Minimising sedation reduces the duration of mechanical ventilation, reduces ICU and hospital length of stay, facilitates early mobilisation and reduces healthcare cost. Additional advantages include a reduced incidence of brain dysfunction (coma or delirium), and a reduction in the need to perform technical examinations (such as CT, MRI or EEG) to assess unexplained changes in mental status. Most ICUs have implemented these insights in their clinical practice. Tapering sedatives might already be beneficial in the early phase after ICU admission, as the early sedation depth already independently predicts delayed extubation and increased mortality (Shehabi et al. 2012).

Unfortunately, most of these studies have not included acute brain injury patients, and specific large randomised clinical trials in the neuro-ICU population are lacking. On the one hand, neurocritical care physicians prefer to avoid unnecessary sedative drugs as much as possible, as they interfere with the neurological evaluation of the patients. An expert panel on the neurological examination of critically ill patients strongly recommends to daily interrupt or to reduce sedation in mechanically ventilated patients, in order to enhance neurological examination and improve short- and long-term outcomes, but advocates against this approach in patients with intracranial hypertension (Sharshar et al. 2014). On the other hand, sedatives are often prescribed in the neuro-ICU, sometimes in a continuous way, to control agitation, to reduce cerebral metabolism, to treat refractory seizures, to treat or prevent intracranial hypertension, to allow for mechanical ventilation to control $PaCO_2$ to facilitate temperature management or to control paroxysmal sympathetic hyperactivity. This widespread use, however, is not supported by evidence from randomised clinical trials. In the absence of such trials, it is important to understand how sedatives can possibly have a major impact on the outcomes of patients.

Current Sedation Practices in the Neuro–ICU

The fact that sedatives are frequently used in the neuro-ICU is demonstrated in several post-hoc analyses from clinical trials or surveys: 77 to 90% of patients were under sedation in the first days of ICU stay after traumatic brain injury (TBI) (Hukkelhoven et al. 2002; Beretta et al. 2011). A recent survey of sedation practices in all 16 Scandinavian neurocritical care centres, over a ten-year period from 1999 to 2009 (Skoglund et al. 2013), demonstrated that over this decade, sedation practice had not changed much, and only half of the centres performed daily wake-up tests.

Daily Wake–Up Test and Analgo–Sedative Protocols in Practice

To date, the role of the daily wake-up test in the neuro-ICU is unclear. Only three small observational clinical studies have looked at the effect of the wake-up test on monitored parameters in acute brain injury patients (Skoglund et al. 2009; Helbok et al. 2012; Skoglund et al. 2014). Although, on average, the daily wake-up test appeared safe, with only a small increase in intracranial pressure (ICP) in the majority of patients, several patients after subarachnoid haemorrhage (SAH) and TBI developed potentially dangerous episodes of intracranial hypertension with reduced cerebral perfusion pressure (CPP) (Skoglund et al. 2009). In selected TBI patients these episodes occurred to a lesser extent and without changes in more advanced neuromonitoring parameters such as microdialysis, jugular bulb saturation and brain tissue oxygenation (Skoglund et al. 2014). In a prospective study conducted in 82 patients with various causes of acute brain injury (Helbok et al. 2012), one-third of the wake-up tests had to be aborted because of important side effects including ICP crises (>20 mmHg), agitation or systemic desaturation. This study also looked at the potential benefit of the wake-up test to detect a new neurological deficit, and found that this was the case in only one patient. All three studies were underpowered to study clinical outcome, and it is impossible to perform a benefit/risk analysis based on these small trials.

Reducing the amount of sedation can also be obtained through analgo-sedative protocols. An example of such a protocol for the neuro-ICU has been proposed, where analgesics (remifentanil for short-term use and fentanyl for long-term use) are to be used as first-line agents, followed by sedatives titrated to sedative scores (first propofol, supplemental midazolam as needed and barbiturates for refractory intracranial hypertension) (Egerod et al. 2010). In a before-after implementation study, this approach led to more pain-free patients, a reduced use of propofol and midazolam, an increase in remifentanil and fentanyl use and a faster awakening of patients without an increase in the duration of sedation or in the incidence of unplanned extubation.

Choice of Sedative

The ideal sedative in the neuro-ICU reduces the metabolism of the brain ($CMRO_2$) while maintaining the coupling between cerebral blood flow (CBF) and $CMRO_2$, does not augment ICP,

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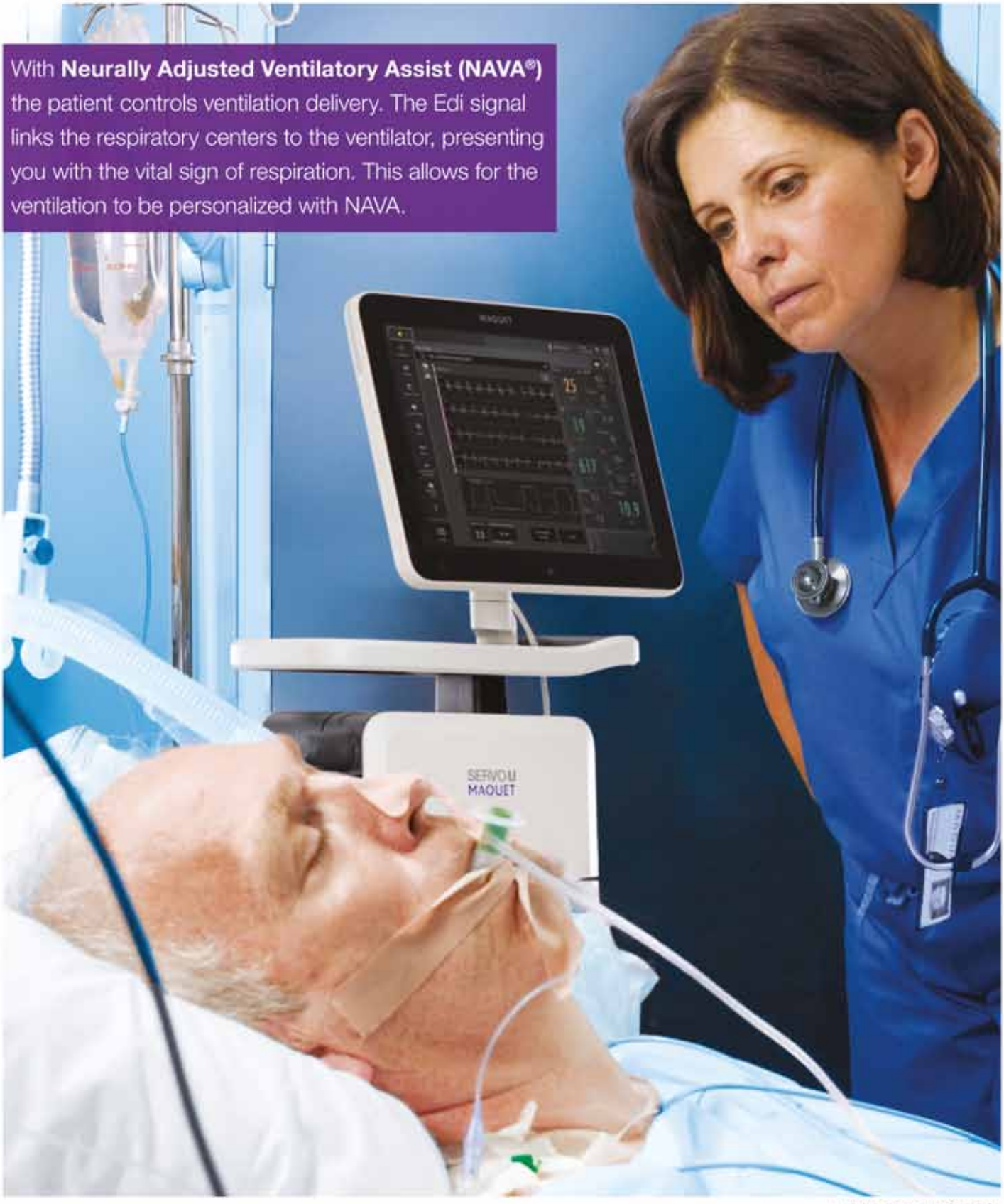

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maintains CPP, has no effect on cerebrovascular autoregulation, is anti-epileptic, short-acting and predictable (Albanèse et al. 2004). Unfortunately, such an ideal sedative does not appear to exist.

Synthetic opioids only have a minor effect on ICP and mean arterial pressure (MAP), although after induction a small and short increase in ICP and a decrease in MAP can be observed (Albanèse et al. 1999). Remifentanil has the advantage of being short-acting with predictable kinetics, and therefore could be first choice in those patients where early clinical assessment is important.

The most frequently used sedatives in the neuro-ICU are propofol and midazolam. The properties and drawbacks of both medications are well known. Propofol is rapid-acting, predictable and reliable, with fast awakening even after prolonged infusions. It reduces brain metabolism, with an associated reduction in CBF and ICP, and acts as an anticonvulsant. Propofol has important haemodynamic side effects. Particularly in the neuro-ICU, there are concerns about propofol infusion syndrome, and hence the dose and duration of propofol should be limited. Of the benzodiazepines, midazolam is the most frequently used. Midazolam has only minor haemodynamic-depressing effects, and reduces brain metabolism, CBF and ICP (albeit with a smaller effect than propofol). As with all benzodiazepines, midazolam is an anticonvulsive drug. After a prolonged infusion, the pharmacokinetics and thus the recovery become highly unpredictable, which is a major drawback in the neuro-ICU setting. In addition, benzodiazepine administration is an important and potentially modifiable risk factor for the development of ICU delirium (Pandharipande et al. 2006). A recent meta-analysis of 13 small randomised clinical trials, encompassing in total 380 TBI patients (Roberts et al. 2011) could not demonstrate convincing evidence that one sedative agent would be more efficacious than another. The authors concluded: "Insufficient data exist regarding the effects of sedative agents on neurologic outcome or mortality."

> **"The use of sedatives in the neuro-ICU remains a dramatically under-researched field"**

The N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has long been banned in brain-injured patients, following earlier claims that it could possibly increase the ICP. However, several prospective observational and interventional trials have been able to demonstrate that these claims are false. In fact, in patients after TBI, ketamine either did not influence ICP (Bourgoin et al. 2005), resulted in a small but clinically insignificant increase in ICP accompanied with an increased CPP (Kolenda et al. 1996) or even significantly decreased ICP (Albanèse et al. 1997; Bar-Joseph et al, 2009).

Dexmedetomidine is a sedation agent targeting alpha-2 adrenergic receptors located in the locus coeruleus nucleus of the brainstem. It is approved for mild sedation. The main side effects of dexmedetomidine are hypotension and bradycardia. In a general ICU population dexmedetomidine provides a safe and effective sedation for patients who are less deeply sedated and thus more cooperative. At the same time dexmedetomidine reduces the incidence and duration of ICU delirium, as compared to propofol or benzodiazepines. In the neuro-ICU, only few data on its clinical use currently exist. A couple of small observational trials in neurosurgical patients indicate adequate sedation, with either no impact on or a reduction of ICP, although there are some concerns regarding hypotensive episodes (Aryan et al. 2006; James et al. 2012).

Sedatives and Neuroregeneration/ Neuroprotection

In critical brain-injured states sedatives are often given in order to reduce the metabolism of the brain, with the purpose of creating the optimal circumstances for the

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brain to recover. It is unclear whether sedatives possess specific neuroprotective properties with an impact on the outcome in these patients. Animal studies in experimental TBI in rats have indicated that midazolam as well as propofol have a negative impact on neuroregeneration and neurocognitive outcomes (Hertle et al. 2013; Thal et al. 2014). It is clear that these results cannot be extrapolated to the human TBI setting, but these studies suggest that the impact of sedatives on outcome is not necessarily positive, and that further research is needed to further explore these findings.

Cortical spreading depressions (CSD) are depolarisation waves that propagate across the grey matter of the brain at low velocity, and are associated with perturbations of the brain ion homeostasis and the efflux of excitatory amino acids. It is hypothesised that CSD might contribute to secondary brain injury after SAH or TBI. In a small non-randomised study, ketamine was effective in stopping CSD (Sakowitz et al. 2009). A more recent retrospective study demonstrated that, of all sedatives, only the administration of ketamine was independently associated with a reduction of CSD, and that midazolam anaesthesia was even associated with an increased incidence of CSD (Hertle et al. 2012). The hypothesis that blocking CSD through NMDA antagonists could improve the outcome in brain-injured patients will be further examined in ongoing studies.

Conclusion

The use of sedatives in the neuro-ICU remains a dramatically under-researched field. In spite of that, sedatives are still frequently used in a continuous way. Attempts to reduce sedation through analgo-sedative protocols appears to be promising, but there are concerns about the risk versus benefit of daily sedative stops. Propofol and midazolam are still the most frequently used sedatives. There is a potential role for ketamine and dexmedetomidine in brain-injured patients. The specific effects of the different sedatives on neuroprotection or neuroregeneration warrant further research. ■

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ICU-RELATED DYSPHAGIA

EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSTICS AND TREATMENT

Due to malnutrition and aspiration dysphagia in critically ill patients on the ICU is an extremely important symptom with crucial impact on outcome and mortality. A broad variety of pathogenetic factors can lead to severe dysphagia in non-intubated and intubated patients followed by a significant delay in decannulation after weaning from the respirator has been completed. The aim of the following review is to present the diversity of pathogenetic factors on the ICU, evaluate the existing diagnostic procedures and, based on current knowledge, give pragmatic recommendations for the diagnostic approach as well as for the further nutritional management of ICU patients.

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In intensive care medicine dysphagia is an extremely frequent and outcome-relevant symptom. Studies on internal medicine, anaesthesiological and surgical intensive care units have shown that 50 to 70% of patients on these wards suffered from dysphagia (Ajemian et al. 2001; Skoretz et al. 2010). In a recent study on a neurological intensive care unit there was even a dysphagia incidence of over 90%, and dysphagia persisted in half of the patients until the day of discharge (Macht et al. 2013). Of particular relevance is the finding that dysphagia in intensive care patients is more severe and in 10-20% of the patients accompanied by silent aspirations (Ajemian et al. 2001, Barquist et al. 2001, El Solh et al. 2003). Regardless of the diagnostic spectrum analysed, dysphagia in critically ill patients is a significant predictor of complications, especially aspiration pneumonia and reintubation, and a crucial determinant of the duration of hospitalisation and the patients' outcome (Macht et al. 2011).

Aetiology and Pathophysiology of Dysphagia on the ICU

The causes of dysphagia in the critically ill can be differentiated into three aetiological categories. Thus, dysphagia may be:

(i) associated with the main diagnosis leading to ICU treatment;
(ii) the result of co-morbidities;
(iii) associated with the treatment on the ICU itself.

Especially in patients on the neurological intensive care unit a combination of the different aetiologies must be expected.

(i) Diagnosis-Associated

As shown in Figure 1, various neurological disorders that typically require treatment on the ICU impair the functionality of the swallowing network or the associated downstream nerves and muscles. Stroke and inflammatory diseases of the CNS lead, depending on location, to disturbance of the supramedullary or medullary control of swallowing. Guillain-Barré syndrome (GBS), critical illness neuropathy (CIP) and critical illness myopathy (CIM) cause dysphagia due to an impairment of motor and sensory cranial nerve function. Finally, disorders of swallowing muscles themselves, as they can be observed in inflammatory myositis, as well as disorders involving the neuromuscular junction, lead to myogenic dysphagia.

(ii) Caused by Co-Morbidities

Apart from the main diagnosis (e.g. acute stroke, GBS, brainstem encephalitis), co-morbidities also play an important role. A wide range of neurodegenerative (e.g., Parkinson's disease, Alzheimer's disease), neurovascular (stroke, subcortical arteriosclerosis encephalopathy) or neuromuscular disorders (polymyositis, ALS) should be mentioned. These disorders are either associated with pre-existing dysphagia, or at least increase the likelihood of a deterioration of swallowing function during ICU treatment. Thus, although hospitalisation on the ICU may be initiated because of e.g. urosepsis or myocardial infarction, the further clinical course gets complicated because of decompensated dysphagia.

(iii) ICU Treatment-Related

Dysphagia in the ICU may also be caused by the treatment itself and/or further environmental conditions. There are six pathomechanisms to differentiate as shown in Figure 2 (Macht et al. 2013).

1. The endotracheal tube, the tracheal cannula, laryngeal masks and nasogastric suction probes can lead to various injuries of the pharynx, larynx or oesophagus.
2. Intensive care patients often develop a weakness of the swallowing muscles due to critical illness neuropathy and myopathy.
3. The development of oropharyngeal and laryngeal sensory deficits. Among other reasons this may be the result of sensory nerve damage due to CIP or because of local mucosal oedema followed by a disruption of the sensory feedback.
4. Qualitative and quantitative impairment of consciousness, either as an effect of sedating medication or as a result of delirium, are also involved in the development of dysphagia.
5. Gastroesophageal reflux in critically ill patients causes insufficient supply of nutrients and is in particular a main risk factor for aspiration.

6. Patients on the ICU often suffer from a desynchronisation of breathing and swallowing. Both the duration of the swallowing apnoea, as well as the coordination of the respiratory cycle and the moment of swallowing may be impaired, increasing the risk of aspiration (Shaker et al. 1992, Gross et al. 2009).

Diagnostic Workup

Dysphagia plays an important role on the ICU. Adequate diagnostic procedures should help to detect this disorder as precisely and timely as possible. Based on the result of swallowing assessment appropriate nutritional management and treatment strategies have to be defined. This section describes a workflow applicable to the ICU.

Screening Tests for Aspiration

The aim of dysphagia screening on the ICU is to identify patients at risk of aspiration, and subsequently to initiate preventive measures and to plan further diagnostic procedures. To this end, water swallowing tests are usually implemented. As a common feature of several different published protocols, the patient is asked to swallow a defined amount of water, while the investigator looks for clinical signs of aspiration (change in voice, cough, stridor) (Cassier-Woidasky et al. 2012). However, these tests usually do not have sufficient sensitivity and/or specificity (Bours et al. 2009) to be propagated as a stand-alone solution. In addition silent aspiration, a key factor in the critically ill, cannot be detected by these tests (Noordally et al. 2011). Finally it should be noted that in many critically ill patients a water test is not feasible due to their clinical condition, so that in the end both the validity and the feasibility of these water tests in the ICU are significantly limited.

Clinical Examination

The clinical swallowing examination by an appropriately trained speech therapist is the most frequently used diagnostic modality for the evaluation of dysphagia on the ICU. This typically involves examination of the oropharyngeal structures as well as swallowing tests with different consistencies (Warnecke and Dziewas 2013). As with aspiration screening, the sensitivity, specificity and reliability of the clinical swallowing examination are also questionable (McCullough et al. 2000; 2001). Hales et.al. (2008) found in a prospective study of 25 tracheotomised ICU patients a sensitivity of only 66% for the detection of aspirations with a clinical swallowing examination. Therefore the management of dysphagia on the ICU cannot be guided solely by clinical tools.

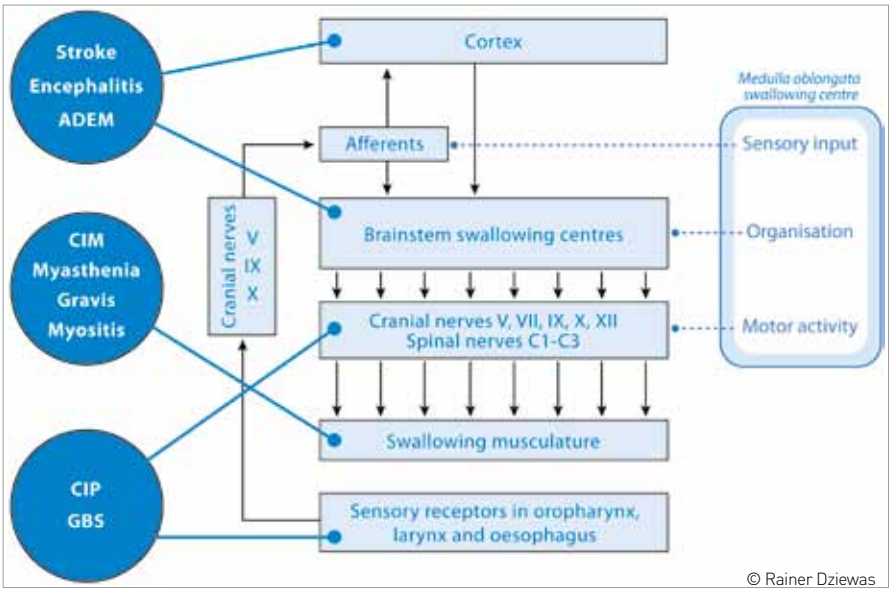

Figure 1. Neurological Disorders that Typically Require Treatment in the ICU

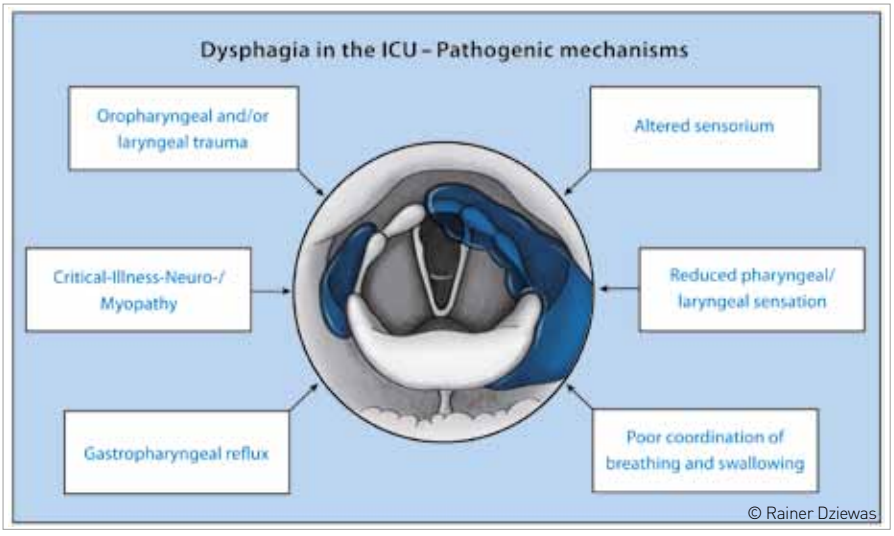

Figure 2. Pathomechanisms of ICU-Related Dysphagia

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

During FEES a flexible naso-pharyngo-laryngoscope is introduced transnasally into the pharynx for direct visualisation of the swallowing act.
FEES aims to:

(i) identify pathological movement patterns;
(ii) evaluate the effectiveness and safety of the swallow process, and
(iii) recommend appropriate food consistencies as well as special diets or swallowing techniques on an individual basis.

Available data indicate that FEES is a well-tolerated and safe examination. In 6,000 investigations only 222 (3.7%) had to be stopped at the patient's request (Langmore 2001). The most commonly reported side effect was self-limited nosebleed being present in approximately 1% of cases. More serious events like vasovagal syncope and laryngospamus occurred in 0.03% (Aviv et al. 2000; Aviv et al. 2001; Cohen et al. 2003). These results were replicated in a group of acute stroke patients. Although the rate of self-limited nosebleed was with 6% higher than in the other studies, no serious side effects were reported, and vegetative symptoms like heart rate and blood pressure fluctuations were mild (Warnecke et al. 2009a). Meanwhile numerous studies have shown that FEES is equivalent to

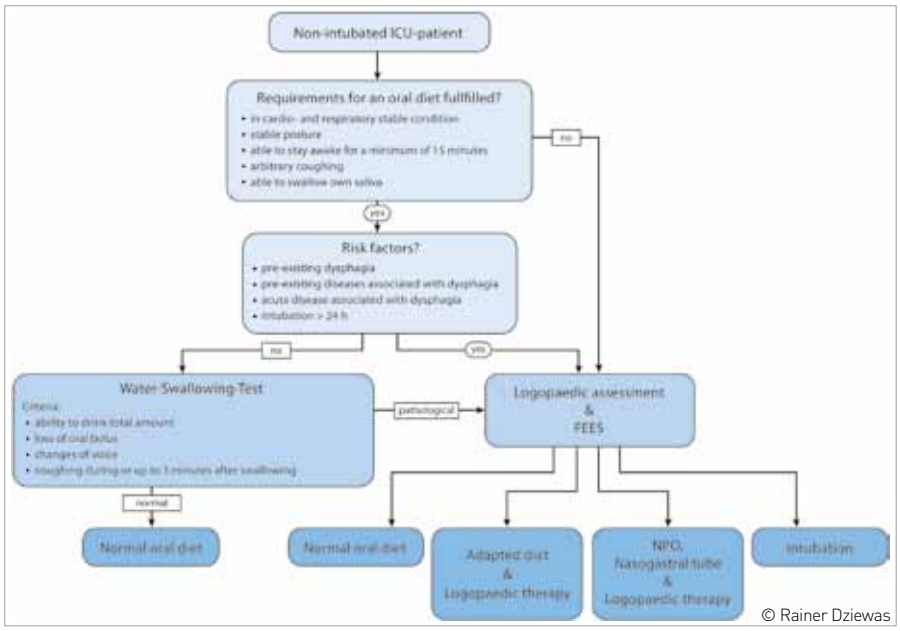

Figure 3. Diagnostic Algorithm for the Assessment of Dysphagia in Non-Intubated ICU-Patients

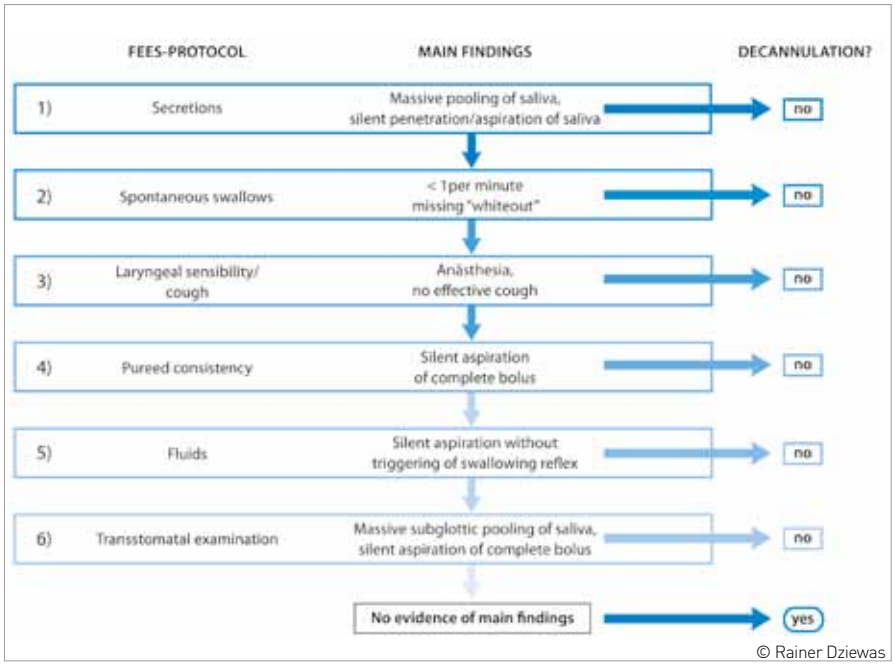

Figure 4. FEES Protocol for Tracheostomy Decannulation.
FEES: fiberoptic endoscopic evaluation of swallowing.

the historic gold standard, the videofluoroscopy (VFSS=Videofluoroscopic Swallow Study) in detecting the most important critical findings like aspiration and residues (Wu et al. 1997; Kelly et al. 2006; Kelly et al. 2007). FEES is also an extremely reliable method, which is underlined by an interrater consensus of over 90% in various studies (Leder et al. 1998; Dziewas et al. 2008).

On the ICU the essential practical advantages of FEES over VFSS are:

- the examination can be done at the bedside, and patients with highly restricted motor functions as well as bedridden or uncooperative patients can be examined.
- repeated follow-up examinations are safely possible without the issue of radiation exposure.
- saliva management can be assessed directly (Langmore 2003).

As has been shown in a large observational study, FEES in daily practice on the ICU is indeed helpful to assess airway protection and to steer dysphagia management (Hafner et al. 2008). Altogether 913 endoscopic swallowing evaluations were performed in 553 patients over a period of 45 months at several intensive care units. Based on the result of FEES, 6.3% of the patients were tracheotomised to protect the airway, 49.7% received a feeding tube and 13.2% a PEG to ensure enteral feeding. In 30.7% of patients oral diet was judged to be feasible. Two other studies showed that in acute stroke the endoscopic evidence of saliva aspiration is a strong predictor for the need for intubation later on (Dziewas et al. 2008; Warnecke et al. 2009b). These results underline the need for early instrumental dysphagia assessment in the critically ill.

Diagnostic Algorithms for the Management of Dysphagia in Non-Intubated and Trachotomised ICU Patients

The Non-Intubated Patient

In non-intubated ICU patients dysphagia assessment provides important information for the selection of the appropriate diet and also guides the initiation of further protective and rehabilitative measures. Although there is currently no standardised algorithm that has been evaluated in prospective studies, the one proposed in Figure 3 considers the advantages and disadvantages of the various diagnostic modalities and implements existing knowledge in order to give pragmatic recommendations. First, minimum basic requirements for an oral diet such as a sufficient state of vigilance and trunk stability are evaluated. Next, the risk factors for dysphagia are assessed. Apart from the patient's main diagnosis specific co-morbidities need to be considered. Since dysphagia is at least in part frequently a side effect of the ICU treatment itself, the duration of intubation and artificial ventilation with a cut-off value of 24 hours is introduced as an additional criterion. In case there are none of these risk factors present, for example in a patient with an uncomplicated surgery followed by quick extubation, it is sufficient to carry out a simple aspiration screening. If this test is normal the patient may directly get an oral diet. If at any of the three steps the just described indicators of dysphagia are present, a clinical swallowing examination by a speech therapist and, ideally, a FEES should be performed. With the help of these diagnostic procedures a decision whether the patient can receive a normal oral diet, requires a special consistency-adapted diet, is in need of tube feeding or should be considered as a candidate for intubation to secure the airway can be made.

The Tracheotomised Patient

The tracheostomy, in particular the minimally invasive dilatational approach, is now a standard procedure on most ICUs, and the majority of long-term ventilated patients are ventilated through this airway access. After successful weaning from the respirator the question arises whether the removal of the tracheal cannula can be achieved. Due to the limitations of the clinical swallowing examination assessment of the swallowing function in this context should include FEES (Warnecke and Dziewas 2013). To increase the reliability and reproducibility of the endoscopic examination, a standardised, step-by-step approach might be implemented (Warnecke et.al. 2013) (see Figure 4). After suctioning pharyngeal secretions and deflating the tracheal cuff the extent and localisation of salivary retentions are assessed and the spontaneous swallowing frequency is observed. If massive pooling or silent aspiration of saliva is visible (**step 1**), the investigation is stopped at this point. If not, the number and efficiency of spontaneously occurring swallows is rated for at least two minutes (**step 2**). If more than one efficient swallow per minute occurs, the investigation proceeds and laryngeal sensibility and cough reflex are tested by gently touching the aryepiglottic region with the tip of the endoscope (**step 3**). Patients demonstrating an efficient cough are given a teaspoon of purée consistency (**step 4**). If no aspiration occurs, the patient is given a teaspoon of coloured water (**step 5**). Silent aspiration of the water, without triggering the swallowing reflex, also indicates lack of readiness for decannulation; otherwise, having swallowed successfully, the patient is regarded as being able to sufficiently protect his/her airway and the tracheostomy tube may be removed immediately. After that, the endoscope is briefly inserted through the stoma, flexed upward to visualise the subglottic structures and downward to inspect the lower trachea, in order to ensure that there are no structural abnormalities comprising the airway (Donzelli et al. 2001). The application of this algorithm in 100 tracheotomised patients who were weaned from the ventilator on a neurological ICU allowed safe decannulation in more than half of the patients (Warnecke et al. 2013). In the further course of treatment only one patient had to be recannulated. Noteworthy also was that the clinical swallowing examination, which took into account the parameters state of vigilance, cooperation skills, saliva swallowing, coughing and amount of collected saliva from the tracheal cannula, would have allowed decannulation in only 27 patients.

"Dysphagia in critically ill patients is a significant predictor of complications..."

Acknowledgements

This article has been modified and shortened compared to Dziewas R, Glahn J (2015) Schluckstörungen auf der Intensivstation. In: NeuroIntensiv. Heidelberg: Springer, pp: 108-14.

All Figures were designed by Heike Blum, Department of Neurology, University Hospital Münster, Germany. ■

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INFECTIONS IN THE IMMUNOSUPPRESSED AND IMMUNOCOMPROMISED PATIENT

A PRIMER FOR INTENSIVISTS

Rapid medical, surgical and pharmaceutical advances have resulted in a burgeoning population of patients with impaired immune function. Intensivists require a succinct clinical approach to assess a patient's immunologic function and subsequent risk for infection in order to prescribe timely and appropriate therapy. This review focuses on the biological basis for immune dysfunction and the clinical assessment of this group of patients.

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Over the last decades the number of immunocompromised patients has increased in parallel with improvements in transplantation science and alongside the development of numerous new classes of immunosuppressive agents offering novel therapy for a wide range of diseases. For example, an estimated 114,690 solid organ transplants were performed globally in 2012 (Global Observatory on Donation & Transplantation 2014). This growing population, however, also represents an increasing number of at-risk hosts. Of great concern, the incidence of serious infections and severe sepsis has clearly increased over time (Martin et. al. 2003).

For clinicians and their patients, recognition of the immunocompromised state is imperative. Infections in such patients can involve unusual organisms requiring atypical pharmacological therapy. In addition to having increased susceptibility to common community-acquired and nosocomial pathogens, immunocompromised patients are vulnerable to opportunistic pathogens (e.g., *Cryptococcus*, *Candida*, and *Aspergillus* species) and to reactivation of endogenous but latent organisms (e.g., *Herpesviruses*, *Toxoplasma gondii*, *Pneumocystis jiroveci*) (Tables 1 and 2). Infection in immunocompromised patients with these pathogens can present with minimal signs and symptoms or with atypical features in unusual locations. This can considerably delay the diagnosis if the presence of immunocompromise is not appreciated. Although the risk of mortality is high in these patients given the underlying immunosuppression and the unusual nature of the involved organisms, outcome can be optimised by early diagnosis and aggressive treatments with specific pharmacotherapy.

An understanding of terminology is important. An immunocompromised patient is one in whom any aspect of host defence is deficient. In contrast, immunosuppression occurs when immune defences are specifically impaired. The approach to infections in the immunocompromised patient can be straightforward even though the variety of infections that can be encountered is quite broad. First, the likelihood of a given opportunistic infection is typically related to the nature, severity and duration of the immune deficit. Finally, the duration of the immune deficit also helps define the probable infecting agents.

A basic understanding of the elements of host defence and immunity is required to appreciate the likely cause of infection in any given immunocompromised patient. Both specific (immune) and nonspecific (non-immune) host defences exist. Nonspecific defence elements include intact integumentary barriers. Defects of the integument such as seen in burns, severe eczema, or some forms of chemotherapy effectively denude the body of its primary defence against the normal microbial milieu. Similarly, invasive intravascular catheters, intubation, trauma and operative procedures disrupt the normal barriers to microorganisms.

Specific immune defects can be categorised into 4 clinically relevant groups. The first involves polymorphonuclear leukocytes (PMNs), which are responsible for phagocytosis and killing of extracellular microbes. The most common defect of PMN function is related to their absence. The second broad group of immune defects involves cell-mediated immunity. This term encompasses processes by which intracellular pathogens as well as malignant and virus-infected cells are eliminated. Cell-mediated immunity involves monocytes/macrophages and T-lymphocytes. The third clinically relevant category of immune defects involves the humoral arm of the immune system. Humoral immune

function involves B-lymphocytes that clonally proliferate to produce appropriate specific antibodies to foreign antigens. Anatomical or functional asplenia results in an immune defect similar to that seen with humoral deficits. The final category of immune defects involves the complement cascade, which is one of the major amplification pathways of the normal immune response.

Infections In Neutropenic Patients

Most patients become neutropenic as a consequence of leukaemia, the treatment of malignancy with chemotherapy, bone marrow transplant, or occasionally due to aplastic anaemia or idiosyncratic drug reactions. Although overt focal processes may occur, fever is the typical presenting feature in most patients with infection and severe neutropenia (<100 PMN/μL). Because of the frequent absence of focal findings, neutropenic patients with fever (>38.3°C) in the absence of a defined infection site must be assumed to have infection. When infection is identified it is usually found in the periodontium, oropharynx, lung, distal oesophagus, colon, perianal area or skin. Bacterial and fungal pathogens dominate in all patients with neutropenia regardless of its cause. Patients with neutropenia secondary to untreated leukaemia/lymphoma or aplastic anaemia are also at increased risk of reactivation of herpes viruses resulting in severe HSV mucositis, disseminated varicella-zoster, and cytomegalovirus (CMV) infection.

The dominant predictors of risk of infection during neutropenia due to chemotherapy are the degree and duration of neutropenia (Klastersky et. al. 1988). Neutropenia due to drug reactions, aplastic anaemia or congenital cyclic neutropenia involves a relatively isolated immune defect without mucosal injury. In contrast, cytotoxic chemotherapy impairs mucosal integrity and phagocytic function of surviving neutrophils and also adversely affects both humoral and cell-mediated immunity. When fever and infection occur in the first few days (<1 week) of neutropenia, gram-positive cocci are frequently responsible. In those with more prolonged neutropenia, gram-negative bacilli become problematic in the second and third weeks. After 3 weeks of neutropenia, there is an increase in the incidence of opportunistic fungal infections, particularly with *Candida* and *Aspergillus* species and more exotic pathogens such as *Mucor* species, *Trichosporon* species and even *Fusarium* species.

Typically, infections in patients with neutropenia are due to endogenous bacteria (although half may be hospital-acquired). Nosocomial acquisition may have occurred from physical contact (gram-negative rods, gram-positive cocci), water sources (*Legionella*) or air (*Aspergillus*). Potential sources of infection with endogenous organisms include skin (e.g., *Staphylococcus* species, coagulase negative *Staphylcoccus* species, *Corynebacterium* species, *Bacillus* species, gram-negative rods, and *Candida*) and gut (e.g., gram-negative rods [*Escherichia coli*, *Klebsiella species*, and *Pseudomonas aeruginosa*] and *Candida* species). In recent decades, organisms such as *Stenotrophomonas maltophilia* causing pneumonia, *Burkholderia cepacia* causing line sepsis and *Aeromonas hydrophila* leading to necrotising fasciitis, *Leuconostoc* species, *Capnocytophaga* species and *Rhodococcus equi* have all emerged as important pathogens. This shift has occurred for a variety of reasons, including use of prophylactic antibiotics and chemotherapeutic regimens causing greater mucositis.

A number of principles, developed in the 1960s, continue to be relevant to the management of fever from an undefined source in the neutropenic host. First, neutropenic patients (PMN count <500 cells/μL) with fever (temperature >38.5°C on one occasion or >38°C on two occasions) should be started on empirical antibiotic therapy (Freifeld et. al. 2011). Second, as a rule, broad empirical antibiotics should be used, particularly in the ICU. Third, broad-spectrum antibiotics should be continued for the duration of the neutropenia or for 10 to 14 days if the absolute neutrophil count (ANC) recovers to greater than 500/μL (whichever is longer). Fourth, the specific choice of the initial antibiotic regimen is dependent on the microbial flora of the local environment. Finally, it is a well-accepted principle of therapy that if fever persists or recurs in a neutropenic patient after 4 to 7 days of broad-spectrum antibacterial therapy, empirical antifungal therapy is required.

Infections in Solid Organ Transplantation Patients

Since 1980 solid organ transplantation success rates have increased dramatically. This improvement has largely been due to the introduction of more potent but selective immunosuppressive compounds as well as advances in surgical technique. Immunosuppression in these patients primarily reflects iatrogenic pharmacologically-induced depression of cell-mediated immunity (cellular immune function) for purposes of graft retention. Pharmaceutical agents that induce defects of cell-mediated immunity include high-dose steroids (>60 mg/day prednisone equivalent), azathioprine, low-dose cyclophosphamide, vincristine, bleomycin, muromonab-CD3), antilymphocyte or thymocyte globulin, and, to a lesser extent, cyclosporine and tacrolimus.

"The approach to infections in the immunocompromised patient can be straightforward"

Post-transplantation infections are divided into 3 major categories based on the post-surgical time period (Fishman 2007; de Pauw and Rubin 2007; Rubin 2002; Rubin et. al. 1981). In the first period, the first month post-transplant, the majority of infections are similar to those in any postsurgical patient. In the second time period, the period from the second until the sixth month post-transplant, opportunistic infections predominate. The third time period, 6 months or more post-transplant, is characterised by infections similar to those in an immunocompetent individual. However, a continuing requirement for high dose pharmacological immunosuppression or the presence of graft versus host disease will substantially alter these timelines.

Most early postoperative infections in solid organ transplant recipients are similar to those occurring in immunocompetent patients; however, their clinical course may be much more severe. Surgical wound and IV catheter infections, urinary tract infections, and pneumonia are typical. Pathogens responsible for these infections are typically nosocomial in origin and will carry resistance patterns endemic to ICU organisms. The majority of remaining early post-transplant infections are caused by reactivation of latent or subclinical infections that were present in the recipient

before transplantation. Reactivation is triggered by perioperative nonspecific insults and intense immunosuppression. Typical organisms include HSV, *Mycobacterium tuberculosis*, geographically restricted mycoses (*Histoplasma capsulatum* and *Coccidioides immitis*) and, occasionally, *Strongyloides stercoralis* and *Toxoplasmosis gondii*. Opportunistic pathogens do not normally present in this early postoperative period, since they require a prolonged period of immunosuppression to manifest.

Following the first month post-transplantation, defects of cellular immunity due to pharmacological intervention begin to have a greater impact on the nature of infections. The risk for infections is maximal between 1 and 6 months (with serious life-threatening infections occurring at 3 to 4 months after transplantation). The immunomodulating viruses (CMV, Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV)) are one of the major infectious concerns during this period. Infection with these viruses can further increase the patient's risk of developing opportunistic infections caused by *Pneumocystis jiroveci*, *Listeria monocytogenes*, *Aspergillus*, *Nocardia* and *Cryptococcus* species.

Normally, at 6 months post-transplantation pharmacological immunosuppression is minimised and graft function is optimal. At this point most infections in graft recipients are similar to those of immunocompetent individuals. The actual organ transplanted is crucial to determining the risk of infection especially in the first three months. For example, lung transplant recipients tend to exhibit recurrent pneumonias, involving both standard bacterial pathogens and opportunistic organisms. Liver transplant recipients exhibit biliary sepsis with increased frequency. Renal transplants are often complicated by recurrent urinary tract infection.

Infections in Haematologic Stem Cell Transplantation Patients

Three broad time periods corresponding to the nature of infectious risk have been defined for bone marrow recipients. The first encompasses the pre-engraftment period occurring from bone marrow ablation until 30 days post-transplant. The second time period, the post-engraftment period lasts from 30 days to 100 days post-transplant. The third time period, the late post-trans-

Table 1. Common Causes of Immunosuppression and Major Infections in Immunocompromised Patients

Immunosuppression		
Defect	**Cause**	**Pneumonia**
Neutropenia	Leukaemia Chemotherapy (doxorubicin, ARA-C, cyclophosphamide) Total-body radiation Idiopathic drug effect Aplastic anaemia	Enteric gram-negative bacilli *Pseudomonas aeruginosa* *Staphylococcus aureus* *Aspergillus* species
Cell-mediated	Hodgkin's disease Lymphoma Corticosteroid use Chemotherapy (azathioprine, vincristine sulfate, bleomycin sulfate) CMV, EBV or HIV infection Protein-calorie malnutrition	*Pneumocystis jiroveci* *Legionella* Herpesvirus (CMV, HSV, VZV) Adenovirus Histoplasmosis Coccidiomycosis *Cryptococcus neoformans*
Humoral	Multiple myeloma Chronic lymphocytic leukaemia Chemotherapy (cyclophosphamide, methotrexate, azathioprine) Splenectomy	*Streptococcus pneumoniae* *Haemophilus influenzae* Enteric gram-negative bacilli
Complement	Congenital deficiency SLE Multiple myeloma	—

Abbreviations: ARA-C, cytosine arabinoside; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV-6, human herpes virus-6b; HSV, herpes simplex virus; MAI, *Mycobacterium avium-intracellulare*; SLE, systemic lupus erythematosus; VZV, varicella-zoster virus.

Table 2. Epidemiologic Risk Categories

Epidemiologic Risk Categories
Community-acquired pathogens
Reactivation of previous infections (either from donor or recipient)
Infections following specific epidemiologic exposures, including food and water, work, recreational activities, pets, zoonotic infections, or sexual activity
Infection specific to donor organ
Iatrogenic or healthcare-associated infections
Specific travel-associated pathogens, including a range of tropical diseases

plantation period, begins 100 days post-transplant (Rubin et. al. 1981; Stamm et. al. 1982; Tolkoff and Rubin 2004; Keiser and Nutman 2004; Barnes and Stallard 2001; Bowden and Meyers 1994; Sable and Donowitz 1994).

In the first time period, infections are primarily related to the severe neutropenia and mucositis caused by the cytotoxic conditioning regimen given for the transplant. Clinical disease and treatment are therefore similar to those for other febrile neutropenic patients. Various prophylactic regimens to prevent infectious complications may be given in this period. These can influence predominant pathogens, shifting bacterial species to more resistant gram negatives, and increasing the incidence of colonisation with fluconazole-resistant *Candida* species. The most common pathogens in this time period include HSV and human metapneumovirus.

The second time period, 30 days to 100 days post-transplant includes infection risk due to antirejection immunosuppressive regimen leading to depressed cell-mediated immunity. However, immune dysfunction caused by the bone marrow ablating conditioning regimen as well as graft versus host disease, may contribute to the increased infection risk during this period. Since allogeneic transplants require greater immunosuppression, they tend to have higher rates of infection than autologous transplants. Because cell-mediated immunity is predominantly affected, infections in this period involve pathogens similar to those seen in organ transplant recipients. The dominant concerns are CMV, herpes simplex virus (HSV) and varicella zoster virus (VZV) (usually reactivation), *Pneumocystis jiroveci*, invasive *Aspergillus*, *Candida species*, rarely HHV-6 and *Cryptosporidum*.

During the third time period, after 100 days post-transplant, VZV reactivation and viral respiratory infections become more common. About 40% of patients will develop a significant VZV infection (either zoster or varicella-like syndrome) during their post-transplant course, and one third will experience disseminated disease associated with high mortality. Potential causes of viral respiratory tract infections in the late post-transplant period include respiratory syncytial virus and parainfluenza. They are the most common causes of viral pneumonia in this population and carry a high mortality rate.

Infections in Patients Receiving Therapy with Biologics

Three groups of biological interventions exist for control of systemic inflammatory diseases. These groups:

1. interfere with cytokine function;
2. inhibit T-cell activation, and
3. deplete B-cells.

The first group contains the current tumour necrosis factor (TNF)-α blocker agents (etanercept, infliximab, adalimumab, certolizumab, golimumab, and natalizumab); the interleukin-1 inhibitors (anakinra); and the interleukin-6 inhibitors (tocilizumab and sirukumab). In the second group, abatacept and belatacept inhibits T-cell activation by preventing T-cell receptors from binding to costimulatory molecules. Rituximab, an anti-CD20 antibody, depletes B cells as a member of the third group.

Data from several large registries consistently have found TNF-α inhibitors to be associated with an increased risk for serious infections, with nearly a 5-fold relative increase in the rate of infections in the first 90 days after starting therapy compared with controls (Bongartz et. al. 2006; Galloway et. al. 2011; Crawford and Curtis 2008). Important bacterial infections include tuberculous and nontuberculous mycobacterial infections; *Listeriosis*, *Legionellosis*, and *Nocardiosis* (Kuehn 2011).

Viral infections such as acute or chronic hepatitis B and C are contraindications to therapy with TNF-α inhibitors because of the risk of reactivation. Reactivation of varicella zoster and CMV is also known to occur. Fungal infections due to *Histoplasmosis*, *Coccidioidomycosis*, *Aspergillus*, *Rhizopus*, and *Cryptococcus* have all been documented. Rituximab has been associated with *Pneumocystis jiroveci* and *Aspergillosis*.

Conclusion

Immunocompromised patients are vulnerable to an exceptionally broad variety of infections. A methodologic assessment of a patient's risk for infection, described above, should assist clinicians in adeptly defining targeted diagnostic testing and therapeutic interventions.

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CLINICAL BENEFITS OF RAPID PATHOGEN TESTING WITH PCR/ESI-MS

Dr. Mark Wilks, Clinical Scientist, Microbiology at Barts Health NHS Trust in London, UK, talks about their experiences of using PCR/ESI-MS technology over a period of 18 months. During its use for the RADICAL study, the department also ran clinical samples of interest through the technology.

Which patient groups could potentially benefit from the PCR/ESI-MS technology?

There are a number of distinct clinical groups for which this technology promises to be quite rewarding, including patients with severe sepsis, pneumonia and compromised immune systems. Patients can be immunocompromised because they have recently had a transplant, or they could be haematology oncology or HIV patients. All the immunocompromised groups tend to be infected with unusual bacteria and fungi, which you might not normally look for. In addition ordinary bacteria, which do not harm immunocompetent people, can have serious consequences in this group.

How would you summarise your experience with this technology?

In general it's been quite an exciting process and one which has caused a lot of interest in microbiology and in different clinical departments in the hospital. In some cases it has been quite difficult to interpret the results, because there has been no technology like this before, so we have no framework with which to base our understanding of the results. It is a steep learning curve. Occasionally we have been baffled by an unexpected organism, one that is quite hard to culture in the laboratory usually.

How does this technology differ to conventional testing and what are its advantages?

There are a number of ways in which it differs from conventional microbiology testing. First is the speed of testing. We are used to a kind of 'gardening' approach, where nothing much happens for a minimum of 18 hours or perhaps 2 or 3 days, whereas with PCR/ESI-MS technology results are available in 6 hours. Another difference is that a lot of bacteria and especially fungi are very difficult to grow and are very slow growing. So with PCR/ESI-MS technology we are getting a lot more positives coming through. With this technology you do not need to try and think of the name of an organism and try to grow it. You rely on the fact that this technology has a very broad coverage and therefore does the thinking for you. You just look for any infectious agent.

How would you recommend using this technology to rule in or rule out infections?

At the moment it is too early to give clear guidance. Obviously if you put the sample through

Direct detection of *Mycobacterium tuberculosis*

1 year old boy with possible septic arthritis in one elbow, but all testing for bacteria and viruses was negative. We tested a specimen of his synovial fluid with PCR/ESI-MS technology, and to our complete astonishment we detected *Mycobacterium tuberculosis*. To make matters more confusing, in the same group of three or four specimens *Mycobacterium tuberculosis* was also detected directly from blood in a 67-year-old male patient in ICU. I was frankly skeptical about the results, thinking that at least one was a contaminant and maybe both were artifacts of some kind! And we repeated the tests several times after cleaning everything with bleach always with the same result. In fact both cases turned out to be genuine. Although the boy had no family history of TB or travel history, he did have an Il12/Tnfα imbalance. There was no question of treating him as the test was not CE marked at the time, but over a month later we grew *Mycobacterium tuberculosis* from his elbow and typing showed that it was in fact Bacillus Calmette–Guérin (BCG) and treatment was started. The 67-year-old male patient on ICU turned out to be a multi-drug resistant tuberculosis patient, which was not known to the admitting physicians.

36-year-old male builder, PMH of lymphoma. Admitted septic, meningitic (first CT scan brain reported normal), one eye was "bulging" and there were cavities on chest x-ray.
Repeat CT Head scan showed possible intracerebral lesions. All conventional microbiology and virology were negative. There was a debate about this being a possible fungal infection or TB meningitis; in fact he was put on quadruple therapy for TB vancomycin, tazocin and ambisome. PCR/ESI-MS of his BAL detected *Consiella* and several other anaerobic bacteria which are hard to grow. The addition of metronidazole to cover anaerobes led to a rapid improvement and probably saved his life. The patient's poor dentition then fitted in with aspiration pneumonia and anaerobic cerebral abscesses, but without the hint we may never have treated the patient in time.

and you get a positive result then it's up to you to decide whether to act on it or not, as with any other test. That is relatively easy compared to ruling out infections where you are relying on the high negative predictive value of the technology to rule out infections. This requires a lot of confidence and experience for people to act on that result and therefore to stop treating and maybe stop looking for further agents.

Why is the high negative predictive value so important in ruling out infections in patients?

The main hope is that we'll have enough confidence in the results to rule out infection. For example, a lot of patients in ICU, who were thought to be septic, actually don't have any infection at all. They might have SIRS, but that could be nothing to do with infection - it could be due to surgery, trauma or another reason. But obviously the possibility of infection has to be considered and treatment may well be started. And there may be no underlying infection at all. What we hope is that our experience so far with ruling out infection will be maintained, and that we will have increasing confidence to act on the results and not to narrow antibiotic treatment or stop antibiotic treatment. In patient groups such as haematology oncology patients there is a huge amount of prophylactic anti-fungal treatment, despite the fact that clinicians don't really have any evidence of the patient having a fungal infection. However, the consequences of not treating an invasive fungal infection are so serious that they dare not take the risk. This has implications for costs as well, if they can rule out having to treat these patients. Barts and London NHS Trust, for example, spends up to two million pounds per year on antifungal treatment, much of which is almost certainly unnecessary.

Another patient group where this high negative predictive value is important is preterm babies, who are admitted to neonatal intensive care units with possible sepsis. Often they are given five days or more antibiotic treatment. The consequences of unnecessary antibiotic treatment are extremely serious. It is not just the question of unnecessary treatments and encouraging antibiotic resistance. It can double their chances of getting necrotising enterocolitis and late-onset sepsis and death. ■

DISCLOSURE:
"Point-of-View" articles are part of the ICU Management Corporate Engagement Programme

NUTRITION MONITORING

Most important when monitoring nutrition is to decide upon the nutritional goal for the individual patient. Technically nutrition balance, indirect calorimetry and blood chemistry are the cornerstones.

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To monitor nutrition is not complicated or difficult. What is more problematic is to monitor nutritional risk and to define the purpose or target for nutrition, especially in the critically ill patient. The present analysis is designed to be useful for nutritional support for critically ill patients admitted to the ICU. The heterogeneity of the patient population is the initial and main problem for nutrition support. However, if nutrition support is individualised, monitoring will be rather straightforward. So the initial step will be to identify the critically ill patients who are at nutritional risk and in whom nutrition makes a difference.

The purpose of nutrition is of course to improve patient outcome. Four general guidelines may be proposed (see Table 1): (i) to identify subjects at nutritional risk, (ii) to avoid nutrition-related complications, (iii) to avoid undernutrition that may lead to an enhanced loss of lean body mass, and (iv) to have a long-term perspective.

Heterogeneity

The heterogeneity of critically ill patients is perhaps best illustrated by the simplistic cartoon in Figure 1. We propose that there are three groups of critically ill patients in relation to nutrition and outcome;

1. those that have a favourable outcome regardless of nutrition,
2. those that have an unfavourable outcome regardless of nutrition and
3. those that may benefit from nutrition, if given correctly.

The groups of patients that are going to have a favourable or unfavourable outcome, regardless of nutrition support, are perhaps not always possible to identify bedside on the day of ICU admission. Conceptually, however, it is important to think in these terms when evidence is evaluated in conjunction with trials investigating nutrition support and outcome. At least retrospectively it is usually possible to identify well-nourished subjects with a very low risk for an unfavourable outcome, as well as subjects with a very low chance of a favourable outcome. If these groups of patients constitute a large proportion of a cohort studied, the chance or possibility to detect a nutrition-related effect on outcome is of course low. It may even result that poor nutrition monitoring and non-individualised nutrition in the high-risk patient cohort induce nutritional risks that totally outweigh the possible benefits.

Another dimension of heterogeneity is the uneven distribution of length of ICU stay. A majority of critically ill patients are short-stayers, while a minority of long-stayers are consuming the vast majority of ICU days. Here differences in case mix and healthcare systems must be considered when the external validity of nutrition studies are discussed. Heterogeneity also comes with the time in the ICU and the variable duration of illness before admission.

Nutritional Risk

The idea of starting with the discussion over heterogeneity is to encourage triage to identify the patients who are at nutritional risk and in whom nutrition matters. It is perhaps not always possible at admission, but within a time period of 4-7 days, they should be identified and subjected to individualised nutrition care including monitoring. Before this time the routines of the unit should focus on "low-risk - maximum benefit interventions".

The evidence that undernutrition may be harmful in critical illness is purely observational. Although malnutrition is associated with unfavourable outcomes in health as well as disease, the predictive value in critical illness is difficult to separate from a number of comorbidities strongly associated with complications and unfavourable outcomes (Moreno et al. 2005).

Table 1.

Nutrition monitoring is a tool to achieve nutrition target.
The following 4 concerns should guide the goal for nutrition.

1. A subject at a nutritional risk
2. Avoid nutrition-related complications
3. Avoid undernutrition that may lead to an enhanced loss of lean body mass
4. Use a long-term perspective

Table 2.

Nutrition monitoring should have the following 3 components. Just as the nutrition target should be individualised, the extent of monitoring should be individualised and most likely modified over time.

1. Nutrition balances (caloric balance, protein balance)
2. Estimation of energy expenditure (best by indirect calorimetry)
3. Blood chemistry

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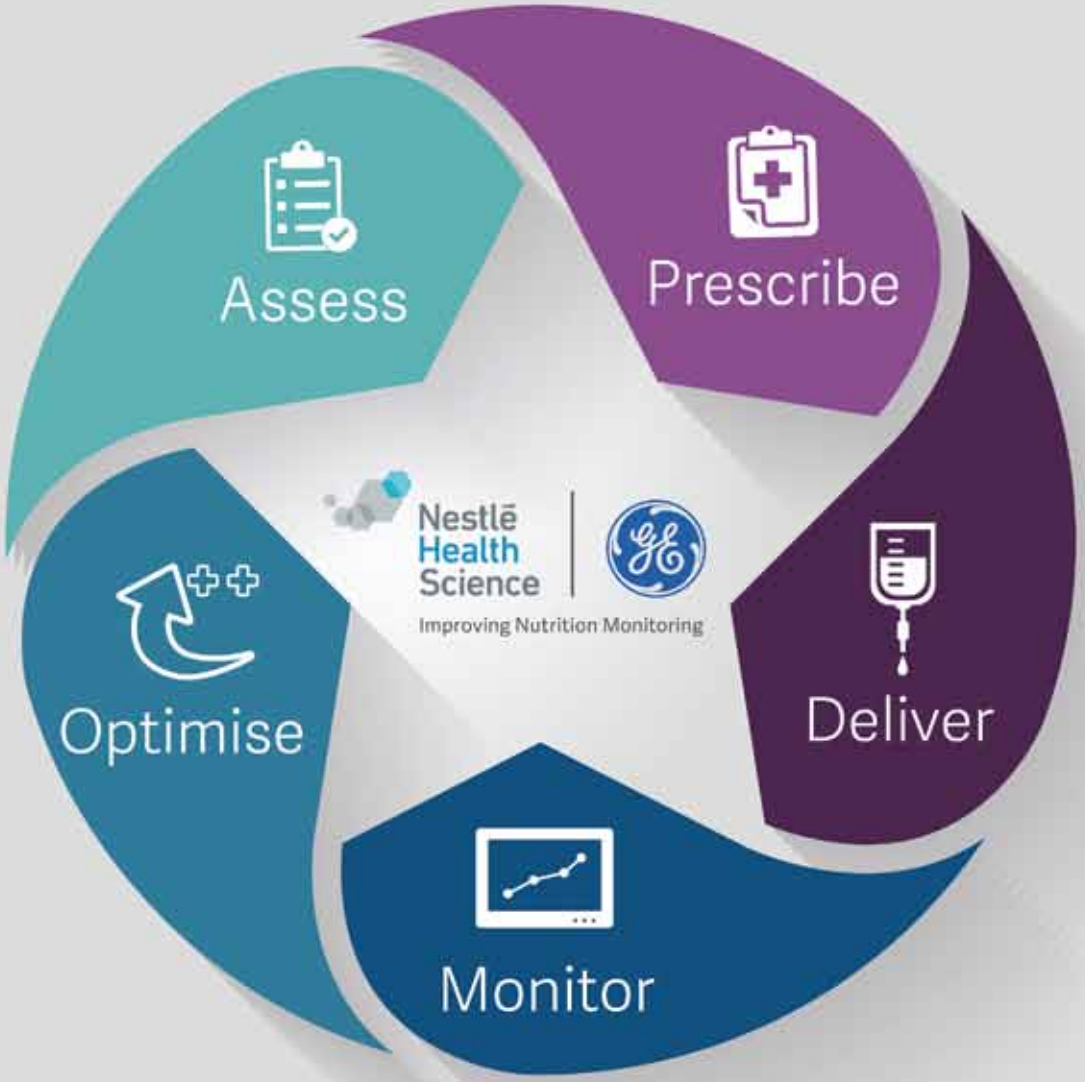

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*Alberta et al.The relationship between nutritional intake and clinical outcomes in critically ill patients: Results of an international multicenter observational study. Intensive Care Med 2009; 35:1728 – 1737

In particular, nutritional treatment of malnutrition in critical illness is perhaps supported by "common sense", but to a lesser degree by evidence. Nevertheless to try to minimise further aggravation of malnutrition for malnourished long-stayers in the ICU is a strategy embraced by most opinion leaders. However, this is a challenging task as this group of subjects is probably also the one most prone to nutrition-related complications. Hence perhaps the group to benefit the most from nutrition monitoring – the present topic.

To identify patients at nutrition risk may be a bedside challenge. Definitions developed for non-critically ill subjects may be of limited help (Kondrup et al. 2003). The Nutrition Risk in Crtically Ill (NUTRIC) score, recently developed for the critically ill, does not separate the risk from malnutrition from the risk from co-morbidities (Heyland et al. 2011). Nevertheless, the NUTRIC score may presently be the best tool to use. It must also be considered that risk related to nutrition status may change over time. A selection of patients considered to be at nutrition risk may be the best use of resources, but this has never been properly demonstrated. Perhaps this level of care should be offered to everybody, but the workload involved should not be underestimated. A close daily evaluation combined with intense monitoring and reconsideration of treatment will consume hours of nurses', dieticians' and doctors' time. Therefore a selection of patients is most probably necessary.

Nutrition–Related Complications

Among nutrition-related complications, overnutrition is probably the most common. This is well known and documented already in the Veterans study, and also from a number of observational reports (Veterans Affairs Total Parenteral Nutrition Cooperative Study Group 1991). The problem when discussing overnutrition is the difficulty in defining it. Most will agree that feeding calories above the energy expenditure is to be considered as overfeeding. This definition, however, contains two problems: 1) energy expenditure is often not known, and 2) it is not self-evident that overfeeding is avoided also when feeding is in accord with energy expenditure. Literature on this topic is not conclusive as cohorts of patients reported are a mixture of short-stayers and long-stayers, with a variable level of nutrition status and finally including subjects in the acute phase as well as a more stabilised phase.

"The heterogeneity of the patient population is the initial and main problem"

It is very difficult to state that overnutrition is avoided without actually measuring energy expenditure, unless an obvious hypocaloric feeding is practised. Hypocaloric feeding may be practised in non-malnourished subjects for a limited period of time (Krishnan et al. 2003). A recent study demonstrated no benefit and no harm from such a protocol, but there is no validity outside the group of relatively young and well-nourished patients actually studied (Arabi et al. 2015).

Figure 1. A cartoon illustrating the fact that the heterogeneity of critically ill patients makes it necessary to define which patients may benefit from a nutrition intervention, patients in the yellow zone. This concern applies both to bedside prescription and to elucidation of the external validity of published evidence.

Individualised Protocol

The basis for individualised nutrition is to have an adequate recording of intake and thereby the possibility to calculate a caloric balance and a protein balance in parallel to the fluid balance practised in most ICUs (Preiser et al. 2015). It is particularly important to also consider non-nutrition calories (the caloric content of solution for antibiotics, sedatives etc.). Still balance calculations can be problematic when considering volume and caloric content of vomit, diarrhoea, and drainages. There may also be concerns over the nutrition value of blood products. Overall it is recommended to not make these balances more complicated than necessary; still when extraordinary intakes or losses are at hand the calculated balance may from time to time be kept in mind. The value of regular measurement of urinary nitrogen losses is debatable, but when a high protein intake on a level above the general recommendations of 1.2-1.5 g/kg/day is practised, the indication also to follow urinary urea excretion as a safety parameter increases. Again, the main difficulty with individualising nutrition and calculation of a correct balance is the determination of the individual's nutritional need.

Caloric Needs

Estimation of the caloric need remains the key question when dealing with a subject at nutrition risk. The use of indirect calorimetry is controversial, but must be considered to be gold standard. The criticism is that reproducibility of measurements is not good enough and that the technique is not open to all patients (those not on mechanical ventilation, with a high oxygen fraction, with airway leakages etc.). But at the end of the day there is probably no better option. In particular for subjects with extremes in BMI it is very difficult to estimate energy expenditure by formulas or by guessing. It is advised to use indirect calorimetry not only in very restricted cases, because there is a learning curve in instrument handling and if used very rarely readings may be less reliable. Repeated readings in subjects at nutrition risk add value when a trend becomes available. Still with the estimated energy expenditure in hand the question remains how to translate this into a calorie number.

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Protein Needs

Recently a number of authors have advocated a high protein (amino acid) intake in critical illness (Hoffer and Bistrian 2012). Again there is no evidence outside observational and retrospective reports, and the same "chicken and egg" matter as for the relevance of an energy deficit exists. Even the guidelines from nutrition societies of 1.2-1.5 g protein per kg and 24h deviate from the recommendations for healthy individuals and are supported by very little evidence (Kreymann et al. 2006, Singer et al. 2009). To recommend an intake above that level without a proper study protocol and nutrition monitoring is not compatible with patient safety.

Long-Term Perspective

The long-term perspective means that after ICU discharge nutritional support must also be considered. It is of course quite meaningless to institute an ambitious nutrition regimen in the ICU, just to abandon it after discharge. Many studies are rightly criticised for evaluating a nutrition intervention during ICU stay in terms of long term (3-12 months) outcomes, without any information of nutrition intake during the post-ICU period (Griffiths et al. 1997; van Zanten et al. 2014). The assumption that non-recorded nutrition is comparable between groups outside the protocolised period is not very convincing. So if a decision is made to individualise nutrition for critically ill subjects at nutritional risk during ICU stay, a post-ICU follow-up plan is also needed. In institutions with a nutrition team, this may come automatically, but otherwise a plan for nutrition should cover the entire period when the subject is considered to be at nutrition risk, both within the hospital, but also in the post-hospital rehabilitation period.

Blood Chemistry

The third cornerstone of nutrition monitoring is to use blood analyses to reflect the metabolism of macro-nutrients. The basis will be blood glucose, plasma triglycerides, plasma urea and plasma ammonia. Frequency of sampling will be related to how the results of these blood tests will be interpreted, to guide prescriptions and/or as safety parameters.

"The use of indirect calorimetry is controversial, but must be considered to be gold standard"

Blood glucose is best available on the blood gas analyses, usually monitored for respiratory purposes (Wernerman et al. 2014). If tight glucose control is practised, hourly measurements are usually necessary, at least in the initial phase. A better understanding of the need of exogenous glucose and the mechanism behind insulin resistance may suggest a more differentiated approach to glucose control related to intake (Soeters and Soeters 2012).

Triglycerides, urea and ammonia are more commonly used as safety monitoring. With very high intakes of protein (amino acids), plasma urea (and also urinary urea) may be used to guide protein dosing. Frequency of sampling in an ICU setting may be each 2nd to 5th day, unless there is kidney or liver failure, which may motivate daily measurements. Elevated plasma triglycerids may motivate restriction of fat intake. This is more common with parenteral fat intake, and the mechanism is not fully understood. Consequently the cut-off level when to reduce fat intake is controversial.

For subjects with extensive external fluid (and tissue) losses, with metabolic conditions, and for extreme long-stayers, a more differentiated testing may be motivated, covering vitamins, trace elements and individual amino acids. Such monitoring should always be individualised, in the extent of testing as well as in frequency of testing (Gagnon et al. 2015).

Conclusion

It is not meaningful to discuss nutrition monitoring unless a target or goal for nutrition treatment is established. To define the goal, the first step should be to decide whether or not the individual patient is at nutritional risk or not. The nutrition should thereafter be individualised, should avoid nutrition-related complications, and should be part of a long-term perspective. Nutrition balance, estimation of energy expenditure, and blood chemistry checks should then be applied according to the goal defined. ■

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CRITICALLY ILL DIABETIC PATIENTS

THE CASE FOR LIBERAL GLYCAEMIC MANAGEMENT

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Background

Several large randomised controlled trials (RCTs) have helped provide evidence to guide clinicians' decisions about blood glucose management in critically ill patients. In two landmark single centre studies, investigators from Leuven reported a reduction in mortality or morbidity with tight glycaemic control (80-110 mg/dl or 4.4-6.1 mmol/L) in critically ill patients (Van den Berghe et al. 2001; 2006). However, the findings of five more recent intensive care-based RCTs, including the very large (>6,000 patients) NICE-SUGAR trial, were unable to replicate these findings (Finfer et al. 2009; Brunkhorst et al 2008; De La Rosa et al 2008; Arabi et al 2008), and in the case of NICE-SUGAR they actually found harm with tight glycaemic control. The aggregate findings of such trials have therefore led to recommendations to target blood glucose levels below 180 mg/dl (10 mmol/L) in order to avoid excessive hyperglycaemia and minimise the risk of hypoglycaemia.

Despite the above consensus, it remains unclear why these trials delivered such disparate and contradictory results. A possible explanation for the discordant findings of glycaemic control trials might relate to the high rate of use of total parenteral nutrition in the Leuven studies (Marik and Preiser 2010; Egi et al. 2011). Given that parenteral nutrition is uncommon in contemporary intensive care units, however, this possibility makes the Leuven studies of unclear modern significance. More importantly, and of relevance to this article, all these randomised studies considered diabetic and non-diabetic patients in the same cohort, and treated such patients in the same way, creating the potential for differing outcomes, because of the variable proportion of such patients and their pre-admission treatment. This uniform approach to glycaemic control in patients with or without diabetes mellitus (DM) may have stemmed from the notion that, even though pre-existing DM has been identified as a risk factor for the development of critical illness, patients with DM have comparable mortality rates to those without diabetes (Stegenga et al. 2010; Vincent et al. 2010), and no specific data existed at that time to suggest that they should be considered unique from the point of view of glycaemic management. Thus general ICU glycaemic control studies have until now influenced the management of glycaemia equally in DM and non-DM patients admitted to ICU. However, this may be unwise.

Current Practice in Diabetic Patients

Because of the above trials, current guidelines recommend targeting blood glucose levels of 140 to 180 mg/dl (7.8 to 10 mmol/L) in all critically ill patients (American Diabetes Association 2012; Ichai et al 2010). These recommendations appear justified not only by the findings of RCTs, but also by multiple observational studies that have demonstrated a higher mortality risk with both hyper- and hypo-glycaemia (Falciglia et al. 2009; NICE-SUGAR investigators 2012; Joeren et al. 2010). We speculate, however, that the ideal glycaemic range might differ in patients with DM, and moreover, even within such a cohort, it may depend on pre-existing glycaemic control. As DM patients comprise approximately 20% of all ICU admissions (Soulimane et al. 2012, Cely et al 2004), the issue of optimal glycaemic control in such patients appears clinically important.

It is important to reflect that in addition to patients with known diabetes, there are other patients admitted in ICU, who have chronic impairment in glycaemia (as shown by HbA1c levels), but in whom a diagnosis of diabetes had not been made prior to hospital presentation. Such patients with "unrecognised diabetes" at ICU admission may also require a specific level of glycaemic control similar to that of patients with known DM. To illustrate this point, in 2014 Plummer et al. described the prevalence of "unrecognised diabetes" in an Australian tertiary hospital as 5.5% of all ICU admissions (Plummer et al. 2014). However, an even higher value of 15% of ICU admissions was reported by a study conducted in Croatia (Gornik et al. 2010), and two American studies (Cely et al. 2004, Hoang et al. 2014) recorded "unrecognised diabetes" in 12% and 13.7 % of ICU admissions respectively. Thus patients with chronic hyperglycaemia (known diabetes and unrecognised diabetes) prior to ICU admission may represent up to 30% of all ICU admissions.

Why Consider a Different Approach to Glycaemic Management Strategy in Diabetic Patients?

The Meaning of Hyperglycaemia

Critically ill patients are at high risk of developing stress hyperglycaemia (Dungan et al. 2009), which is characterised by a high state of hepatic gluconeogenesis, excessive insulin resistance and increase of circulating cytokines, cortisol, epinephrine and glucagone. In patients with diabetes, chronic hyperglycaemia may already exist, and critically ill patients with DM

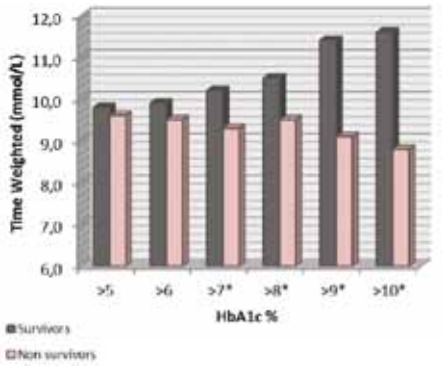

Figure 1. Relationship between HbA1c – Time-Weighted Glycaemia and Mortality

*= Statistically significant (p <0.05)
Source: Data extracted from Egi et al. (2011)

Table 1. Hyperglycaemia and its Associations According to the Presence or Absence of Diabetes

Author	Study setting (patients, n=)	Key findings		
		Total cohort	Diabetics	Non-diabetics
Meyfroidt et al. 2010	n=2,732 1 centre (pooled analysis of the two Van den Berghe studies)			Increasing mortality as mean morning blood sugar increased from 80-110 (4.4-6.1 mmol/L) to >150 mg/dl (8.3 mmol/L)
Rady et al. 2005	n=7,285 1 centre			Increasing mortality as median glycaemia increases from 80-110 (4.4-6.1 mmol/L) to >150 mg/dl (8.3 mmol/L)
Egi et al. 2008	n=49,967 2 centres		No change in mortality with increase from 80-110 to > 200 mg/dl	Steep increase in mortality as glycaemia increases from 80-110 (4.4-6.1 mmol/L) to >200 mg/dl (11.1 mmol/L)
Falciglia et al. 2009	n=259,040 173 centres		Less steep increase in mortality as glycaemia increases	Increases in mortality as glycaemia increases
Egi et al. 2011	n=415 2 centres	HbA1c >7%: mortality decreases with higher glycaemia	Decreased risk if chronic hyperglycaemia	Not applicable
Sechterberger et al. 2013	n=10,320 1 centre		No increase in risk with hyperglycaemia	Mortality increase as glycaemia increases
Krinsley et al. 2013	n=44,964 23 centres		Glycaemia between 110-180 mg/dl (6.1- 10 mmol/L) associated with less mortality compared to 80-140 mg/dl (4.4-7.8 mmol/L)	Glycaemia between 80-140 mg/dl associated with lowest mortality

may simply display slightly or moderately worse glucose derangements.

Among non-diabetic patients, stress hyperglycaemia is associated with an increased risk of mortality after adjustment for illness severity. In particular the risk of death increases in proportion to blood glucose levels (Falciglia et al. 2009; Krinsley et al. 2003; Umpierrez et al. 2002; Finney et al. 2003). In contrast, data from several studies suggest that the adverse outcomes associated with hyperglycaemia are negligible or absent in patients with pre-existing diabetes (Sechterberger et al. 2013; Krinsley et al. 2013; Egi et al. 2008; Egi et al. 2011, Rady et al. 2005).

In all the studies cited above, a strong association between hyperglycaemia (episodes of hyperglycaemia and time-weighted hyperglycaemia) and ICU mortality was consistently found in non-diabetic patients but not in diabetic patients. This lack of association between hyperglycaemia and mortality may relate to the fact that diabetic patients have developed tolerance to hyperglycaemia. Thus diabetic patients may behave in relation to glucose the way patients with chronic obstructive pulmonary disease behave in relation to the correction of chronic hypoxaemia (Joosten et al. 2007), or patients with chronic hyponatraemia behave in relation to the correction of chronic hyponatraemia (Widdess-Walsh et al. 2007), and hypertensive patients relate to the rapid correction of high blood pressure levels (Shuaib et al.1992).

To further understand the importance of chronic hyperglycaemia in diabetic patients and its impact on acute glycaemic management, it is important to appreciate the value of measuring HbA1c. There is a direct relationship between HbA1c and mean glycaemia, because haemoglobin remains glycated during the approximate 120-day lifespan of the erythrocytes. As such a HbA1c of 6% corresponds to a mean plasma glucose level of 7.5 mmol/L (126 mg/dl) in the previous six to nine weeks, and each 1% increase in HbA1c corresponds to an increase of about 2mmol/L in mean plasma glucose levels (Peterson et al. 1998; Rohlfing et al. 2002). By measuring HbA1 in diabetic patients on admission, it is possible to estimate typical glucose levels, and theoretically it should then be possible to aim for type-individualised care (a kind of precision medicine) that seeks to maintain individual homeostasis by aiming for an acute glucose target, which approximates the normal glycaemic control for that diabetic patient prior to ICU admission.

To further understand this concept, Egi et al. (2011) evaluated in detail the interaction between pre-morbid hyperglycaemia, measured by means of HbA1c levels at ICU admission, acute glycaemia as delivered in ICU and hospital mortality. Their findings showed that patients with higher pre-admission HbA1c levels (>7%) were much less likely to die in hospital when their mean glucose concentrations in ICU were >180 mg/dl (10 mmol/L) (see Figure 1). These data support the concept that in the presence of chronic hyperglycaemia (Egi et al. 2011) tolerating higher than normal blood glucose levels can be considered safe and may even be potentially desirable in diabetic patients experiencing hyperglycaemia in the ICU.

In critically ill diabetic patients any consistent difference between premorbid glycaemia and mean glycaemia during ICU admission in the direction of decreased glucose levels could be considered a form of "relative hypoglycaemia". Thus if a patient is used to having, for example, a 180mg/dl (10 mmol/L) blood glucose level, then such a patient may experience the physiological stress of hypoglycaemia at 100 mg/dl (5.5 mmol/L) of blood glucose concentration. Such stress may then be the same as that of a normal person who develops a glucose level of <40 mg/dl (2.2 mmol/L). Such "relative hypoglycaemia" may be a silent contributor to morbidity and mortality in diabetic patients, especially in a context (ICU) where symptoms of "relative hypoglycaemia" are often masked by sedative or analgesic medication.

The Importance of Hypoglycaemia

Hypoglycaemia has deleterious effects in critically ill patients by increasing the systemic inflammatory response (Dotson et al 2008), inducing neuroglycopaenia (Schlenk et al. 2008), inhibiting the corticosteroid response

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Table 2. Studies of Hypoglycaemia in ICU

Author	Study setting (patients, n=)	Key findings		
		Total cohort	Diabetics	Non-diabetics
Kalfon et al. 2015	n=2,684	-severe hypoglycaemia <40 mg/dl (2.2 mmol/L) associated with increased 90-day mortality -moderate hypoglycaemia <60 mg/dl (3.3 mmol/L) not associated with increased mortality -≥3 hypoglycaemic episodes (<60 mg/dl or 3.3 mmol/L) associated with increased mortality	no subgroup analysis	no subgroup analysis
Sechter-berger et al. 2013	n=10,320 single centre	-	-hypoglycaemia occurs more frequently -hypoglycaemia (<40 mg/dl or 2.2 mmol/L) associated with increased mortality	-hypoglycaemia (<40 mg/dl or 2.2 mmol/L) associated with increased mortality
Krinsley et al. 2013	n=44,964 23 centres		-severe (<40 mg/dl or 2.2 mmol/L)) and mild-moderate (40-69 mg/dl or 2.2-3.8 mmol/L) hypoglycaemia associated with increased mortality	severe (<40 mg/dl or 2.2 mmol/L)) and mild-moderate (40-69 mg/dl or 2.2-3.8 mmol/L) hypoglycaemia associated with increased mortality
NICE-SUGAR Study Investigators 2012	n=6,026 42 centres	moderate (41-70 mg/dl or 2.2-3.9 mmol/L) or severe (<40 mg/dl or 2.2 mmol/L) hypoglycaemia associated with higher mortality		
Krinsley et al. 2011	n=6,240 25 centres		-hypoglycaemia (<70 mg/dl or 3.9 mmol/L) associated with higher mortality	-hypoglycaemia (<70 mg/dl or 3.9 mmol/L) associated with higher mortality
Egi 2010 et al. 2010	n=4,946 2 centres	-at least 1 episode of hypoglycaemia (<81 mg/dl or 4.5 mmol/L) associated with higher mortality -increased severity of hypoglycaemia associated with higher mortality	no subgroup analysis	no subgroup analysis
Meyfroidt et al. 2010.	n=2,732 single centre (pooled analysis of the two Van den Berghe studies)	at least 1 episode of hypoglycaemia (<40 mg/dl or 2.2 mmol/L) associated with increased hospital mortality	no subgroup analysis	no subgroup analysis
Hermanides et al. 2010	n= 5,961 single centre	incidence of ICU deaths per 1000 ICU days higher with hypoglycaemia (<45 mg/dl or 2.5 mmol/L)	no subgroup analysis	no subgroup analysis
Krinsley et al. 2007	n= 5,365 single centre	-diabetes associated with increased risk of hypoglycaemia -severe hypoglycaemia (<40 mg/dl or 2.2 mmol/L) associated with increased mortality	no subgroup analysis	no subgroup analysis

to stress (Keller-Wood et al. 1983), impairing sympathetic system responsiveness (Herlein et al. 2006) and causing cerebral vasodilatation (Dieguez et al. 1997). Hypoglycaemia, both severe (<40 mg/dl or 2.2 mmol/L) and mild/moderate (less than 70 mg/dl or 3.9 mmol/L), likely contributes to increased mortality in critically ill diabetics and non-diabetic patients. (Kalfon et al. 2015; NICE-SUGAR investigators 2012; Hermanides et al. 2010).

It seems biologically reasonable to think that hypoglycaemia during critical illness in diabetic patients should be considered in the context of chronic overall glycaemic control. The main aim in DM patients may then be not only to avoid absolute hypoglycaemia, but also to avoid "relative hypoglycaemia", which can be expressed by the "distance" or decrease between chronic glycaemia levels and the blood glucose levels experienced during acute illness. As described above, relative hypoglycaemic episodes for diabetic patients might have the same biological toxicity that absolute hypoglycaemic conditions produce in non-diabetic patients.

Moreover the 'protective' modifications associated with chronic hyperglycaemia leave cells vulnerable to relative glycopaenia, particularly in situations where hypotension and hypoxia co-exist. Some evidence suggests that chronic hyperglycaemia sets up a pattern of cellular conditions that might actually protect against acute hyperglycaemia-mediated damage but exacerbate hypoglycaemia-induced injury. One mechanism for this effect might be the preferential 'down regulation' of insulin independent glucose transporters under chronic hyperglycaemic conditions (Deane and Horowitz 2013).

The Importance of Glycaemic Variability

To define the best glycaemic management in diabetic patients, it is therefore logically necessary to take into account that it is relative dysglycaemia that may require treatment instead of just absolute hypoglycaemia or hyperglycaemia.

Dysglycaemia can be seen to encompass three domains of glycaemic control: hypoglycaemia, hyperglycaemia and glycaemic variability. (Egi et al. 2007). Therefore a trend measure like glycaemic variability has been defined as the standard deviation of mean glucose level during ICU stay or as the difference between highest and lowest glycaemia in an established time period. Diabetic patients have greater absolute glycaemic variability than non-diabetic patients, and this might also affect the different association between glycaemia and outcome (Krinsley et al. 2009).

There is a growing body of evidence to suggest that for non-diabetic patients marked fluctuations in blood glucose are also related to an increased risk of mortality (Ali et al 2008; Meyfroidt et al. 2010; Krinsley et al. 2008; Dossett et al. 2008; Krinsley et al. 2009; Egi et al. 2006). A 2003 study found that in umbilical vein cells glycaemic fluctuations caused a higher level of oxidative stress compared to sustained hyperglycaemia (Quagliaro et al. 2003). This correlation has been demonstrated also in patients with type 2 diabetes. Such increased oxidative stress can result in endothelial dysfunction and can contribute to vascular damage (Monnier et al. 2006).

Despite these concerns, the impact of glycaemic variability in critically ill diabetic patients has not been extensively investigated. In fact, a large study demonstrated that glycaemic variability had an independent association with mortality among

non-diabetic individuals but not among diabetics (Krinsley et al. 2009). Such a finding supports the concept that a degree of spontaneous tolerance to glycaemic variability may occur in diabetic patients due to their glycaemic history prior to ICU admission, which may have included chronic exposure to much greater levels of glycaemic variability than non-diabetic patients.

Thus efforts to maintain glycaemia in the normal range and decrease variability may be potentially injurious for patients with altered premorbid glycaemia. In this regard, a recent study demonstrated that a higher level of Time In Range glycaemia (TIR) (70mg/dl-140 mg/dl or 3.9-7.8 mmol/L) had a positive correlation with decreased mortality in a population of non-diabetic critically ill patients, while, among patients with diabetes, there was no consistent relationship between TIR and mortality (Krinsley et al. 2015).

Table 3. Glycaemic Variability Studies in ICU Patients

Author	Study setting (patients, n=)	Key findings	
		Diabetics	Non-diabetics
Meyfroidt et al. 2010	n=2,732 patients, single centre (pooled analysis of the two Van den Berghe studies)	mortality of patients with mean delta (max–min daily glycaemia) <4 (72 mg/dl), 4–6 (72-108 mg/dl), >6 mmol/L (108 mg/dl) was 10.4%, 23.9%, 28.7%, respectively	mortality increases with increase in delta glycaemia (max-min daily glycaemia)
Egi et al. 2006	n=7,049 4 centres	Subgroup of 728 diabetics from 2 centres. No significant increase in mortality as standard deviation of glycaemia increases	Significant increase in mortality as standard deviation of glycaemia increased
Krinsley et al. 2009	n=4,084 single centre	Mortality not associated with glycaemic variability	Increased glycaemic variability associated with higher mortality
Sechterberger et al. 2013	n=10,320 single centre	ICU mortality and glycaemic variability not associated	Blood glucose variability associated with increased ICU mortality
Krinsley et al. 2013	n=44,964 23 centres	Mortality and glycaemic variability not asssociated	Mortality associated with glycaemic variability increasing (Coefficient of Variation > 20%)

Chronic Glucose Management in Diabetes and its Relevance to Critical Illness

Diabetes is mainly a chronic disease, and so lessons may also be derived from its "chronic" treatment, which have potential relevance to its acute management. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study reported that in type 2 diabetic individuals in the ambulatory setting, aggressive glucose control to reduce glycosylated haemoglobin level from 8.3 to 6.4% over just a few months significantly *increased mortality* compared with control therapy. This means that a reduction of mean glycaemia of about 0.7 mmol/L per month appeared to be injurious. In contrast, the Action in Diabetes and Vascular Disease (ADVANCE study), published at the same time, showed that attempting to reduce glycosylated haemoglobin levels over a much longer period of time (slower decrease in glycaemia which allowed adaptation) was associated with a non-significant downward trend in mortality (Advance Collaborative Group et al. 2008; Gerstein et al. 2008; Dluhy et al. 2008).

There were important differences between ACCORD and ADVANCE in terms of blood glucose, which may be relevant to acute glycaemic management. Firstly, the baseline level of HbA1 was different: ACCORD included patients with a mean HbA1c of 8.1% compared with 7.5% in the ADVANCE study. Secondly, the speed of lowering HbA1c was very different: in the ACCORD study, the HbA1c levels fell to 6.7% within the first 4 months while in ADVANCE the HbA1c decreased to 7% within the first 6 months (a big difference in speed of reduction - such that the rate of decrease in glycaemia was almost 10 times faster in ACCORD). These findings in the chronic setting, showing an association between increased mortality and fast reduction in HbA1c levels, raise concerns that any therapy that leads to a rapid decrease in glycaemia in diabetic patients with high premorbid HbA1c values is dangerous and should be avoided. As such, normalisation of glycaemia in ICU patients with DM and chronic hyperglycaemia may indeed be dangerous.

Conclusions

On the basis of the modern "three domains" paradigm of glycaemic control in the acute setting, diabetic patients are different. In such patients, hyperglycaemia and greater glycaemic variability are not independently associated with increased mortality. Moreover the third domain of hypoglycaemia also appears different. In particular, in diabetic patients with poor pre-admission glycaemic control (chronic hyperglycaemia), even acute normoglycaemia may actually be a form of relative hypoglycaemia and may be associated with increased mortality. The evidence suggests that glycaemic management algorithms should be tailored differently for diabetic and non-diabetic patients and that a more liberal set of targets ("permissive moderate hyperglycaemia") may be justified in diabetic patients. Finally it appears desirable that further studies should investigate optimal blood glucose targets for critically ill diabetic patients in relation to premorbid glycaemia to test the feasibility and safety as well as the possible efficacy of a degree of "permissive moderate hyperglycaemia". ■

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HEART-LUNG INTERACTIONS FROM THE LUNG'S PERSPECTIVE

In this article we describe the characteristics of the interaction between lung protective ventilation and pulmonary and right ventricular function in ARDS. We highlight and discuss the concept that protective ventilation should be directed towards all components of the functional unit, and discuss how mechanical ventilation can modulate the interaction between them.

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The heart and the lungs share a common physical space inside the thorax in which they are anatomically and functionally linked by the pulmonary circulation. These three elements are the main components of a functional unit specialised in fulfilling the physiological task of gas exchange and oxygen delivery. Tidal breathing results in cyclic changes in intra-thoracic pressure that affects the interaction between the components of this functional unit in a complex manner. During normal spontaneous breathing these pressure changes are of low magnitude, ranging from slightly negative (i.e. sub-atmospheric) to slightly positive, resulting in low transpulmonary pressure swings. Such cyclic changes are beneficial as they facilitate venous return and improve the matching between pulmonary perfusion and ventilation. Mechanical ventilation significantly alters this physiological scenario. The baseline operating pressure in the thoracic cavity increases from atmospheric to a continuous positive level, the positive end-expiratory pressure (PEEP). In addition cyclic tidal mechanical ventilation above this new operating level occurs at significantly higher than normal transpulmonary pressures to which the functional unit must adapt. When higher tidal volumes and/or pressures are delivered, especially in pathological conditions such as acute respiratory distress syndrome (ARDS), the adaptation capability of the system is critically challenged. The pathophysiological changes of ARDS, which include inflammation, interstitial and alveolar oedema and loss of lung volume make the functional unit particularly vulnerable to the negative effects of mechanical ventilation. In heterogeneous ARDS lung tidal volume is unevenly distributed, imposing an increased mechanical stress on lung structures, which can be greatly amplified at a regional level where normally aerated areas inflate next to collapsed areas. The resulting ventilator-induced lung injury (VILI) can amplify lung damage (Slutsky and Ranieri 2013). One of the major advances in ARDS management has been the introduction of lung protective ventilation strategies. Aimed at minimising VILI by reducing the delivered cyclic tidal volumes and pressures, they have significantly contributed to reduce mortality to levels around 35-40% (Rubenfeld et al. 2005). However, lung protection has mainly focused on preventing the deleterious effects of mechanical ventilation on the alveolar compartment. However, the impact of positive pressure ventilation on the vascular compartment of the functional unit has received much less attention. This omission is surprising as pulmonary artery hypertension, increased pulmonary vascular resistance (PVR) and right ventricular (RV) failure are pathophysiological components of ARDS and have been known for a long time (Zapol and Snider 1977; Villar et al. 1989; Squara et al. 1998).

Pulmonary Vascular Dysfunction in ARDS

The term pulmonary vascular dysfunction (PVD), introduced more than 30 years ago, (Zapol and Snider 1977) refers to the pathophysiological involvement of the vascular and heart components of the functional unit in ARDS. It can be defined as the increase in pulmonary arterial pressure and/or PVR resulting in different degrees of right ventricular (RV) dysfunction. Causes of PVD include structural factors affecting the vascular component during ARDS, that include: pulmonary vasoconstriction induced by hypoxia and/or vasoactive inflammatory mediators; microvascular thrombotic phenomena; reduced lung volume; interstitial oedema that compresses the microcirculation; endothelial damage due to the direct inflammatory insult and vascular remodelling. PVD should be considered a continuum during the course of ARDS that can range from mild pulmonary hypertension, invariably present in most ARDS patients, to severe pulmonary hypertension with overt right ventricular failure. Clinically the overall estimated incidence of PVD approaches 70% and nearly 20% of ARDS patients evolve to its most severe form, the acute cor pulmonale (Bull et al. 2010; Boissier et al. 2013). Although still under debate (Ryan et al. 2014), there are accumulating clinical data that strongly support an existing link between PVD and ARDS outcome. Direct evidence from recent clinical studies has shown that PVD is independently associated with higher morbidity and mortality (Bull et al. 2010; Boissier et al. 2013). In addition the presence of a high physiological dead space, as an expression of endothelial/microcirculatory dysfunction has consistently shown to be a very strong predictor of mortality in ARDS (Matthay and Kallet 2011). More indirectly the analysis of a large randomised placebo-controlled clinical trial

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on the use of inhaled nitric-oxide concluded that among survivors those who received nitric-oxide had better functional outcomes at six months compared to controls (Dellinger et al. 2012).

Heart–lung Interactions and PVD: The Role of Mechanical Ventilation

Whether the clinical expression of PVD remains as a mild pulmonary hypertension or evolves to acute cor pulmonale depends on the extent of the intrinsic vascular involvement related to ARDS, as described above, but also on the pharmacological (i.e. selective vasodilators) and ventilatory management. The role of mechanical ventilation is of particular interest as it constitutes a potentially modifiable factor that can modulate the interaction between the heart, the lung and the pulmonary circulation. In fact, high tidal volume ventilation has been shown to directly cause (Menendez et al. 2013) or worsen PVD (Vieillard-Baron et al. 1999). In a recent study the increase in driving pressure (i.e. plateau pressure – PEEP) was an independent factor associated with the development of cor pulmonale (Boissier et al. 2013). Interestingly, driving pressure was also recently identified as the isolated ventilation variable that better predicted mortality in the analysis of a large cohort of ARDS patients (Amato et al. 2015). Driving pressure is directly related to the cyclic strain imposed on preserved ventilated units and is expressed as the ratio between tidal volume and lung compliance.

Lung protective ventilation strategies can also potentially prevent the occurrence and progression of PVD (Bouferrache and Vieillard-Baron 2011; Jardin and Vieillard-Baron 2007). The routine use of echocardiography evaluation of the RV in ICU has contributed to the first description of a specific strategy named the RV protective approach (Bouferrache and Vieillard-Baron 2011). This strategy, based on simple and easy to apply rules, combines the use of low tidal volumes (limiting plateau pressure to < 28cmH_2O), low PEEP and the early use of prone positioning. The proponents of this strategy summarised their approach with the assertion: "what is good for the right ventricle is good for the lung" (Repessé et al. 2012), as they found echocardiographic signs of improved RV function in response to such a strategy. Unfortunately, the reported incidence of PVD in the era of lung protective ventilation is still high (Bull et al. 2010; Boissier et al. 2013). Maybe additional factors such as the lung condition expressed by the lung volume status and the characteristics of pulmonary haemodynamics should be taken into account for improving pulmonary vascular-RV protection.

Lung Volume Status

The lung protective effects of using low tidal volumes are strongly supported by clinical and experimental evidence. However, low tidal volume ventilation can be associated with lung collapse, hypercapnia and respiratory acidosis, all of them potentially causing an increase of the pulmonary vascular load on the RV. Lung volume status (i.e. end-expiratory lung volume) may have a particular role in the development of PVD as it affects PVR in a u-shaped fashion (Whittenberger et al. 1960). Low lung volumes can promote lung collapse, which triggers hypoxic pulmonary vasoconstriction, and alters the extra-alveolar vessels' geometry, reducing their diameter and eventually leading to capillary derecruitment. At high lung volumes the compression of alveolar capillaries accounts for most of the increase in pulmonary vascular resistance. During mechanical ventilation lung volume is critically affected by the level of PEEP. Both low levels when associated with lung collapse and high levels when inducing excessive lung inflation increase PVR. These effects are enhanced in the heterogeneous ARDS lung where overinflated lung regions may coexist with sometimes extensive regions of dependent lung collapse. In such a condition, the beneficial effects of low PEEP on pulmonary circulation and RV function could be offset by the negative effects associated with lung collapse, whereas a higher level of PEEP could be beneficial if associated to a recruitment effect. In other words, how PEEP affects lung volume is a major determinant of its haemodynamic effects. This probably accounts for the conflicting haemodynamic responses to PEEP reported in the literature.

> **"Protective ventilation should be good for both lung and the heart"**

Pulmonary Vascular Haemodynamics

To accommodate the entire output of the RV that perfuses the lung, pulmonary vessels are highly distensible, offering a low resistance to forward flow. A low arterial elastance is also essential to maintain RV efficiency, that is the effective transfer of power from the ejecting ventricle to the pulmonary circulation at the lowest energetic cost. This ensures an optimal coupling between the RV and the load imposed by the pulmonary circulation. An increase in pulmonary arterial elastance is probably as important as an elevated PVR in increasing RV load (Milnor et al. 1969). In patients with primary pulmonary hypertension, the ventricular-vascular decoupling caused by an increased arterial stiffness is the hallmark of the shift from a compensated RV dysfunction to right ventricular failure. It is reasonable to think that an increased arterial elastance is also an important component of PVD during ARDS, due to the predominant vasoconstrictive state caused by hypoxaemia, acidosis and vasoactive mediators. Another factor that impairs ventricular-vascular coupling is related to wave reflection phenomena. When the forward pressure (or flow) wave generated by the RV systole meets the backward returning wave reflected from the distal arterial tree, pressure is increased and flow decreased. In the normal pulmonary circulation wave reflection phenomena are minimal and the reflected wave arrives during the ventricular diastolic period. However, in pathological conditions in which arterial elastance or resistance are increased, reflected waves are regularly present and arrive during systole, affecting RV ejection and decreasing RV efficiency. Interestingly, timing of reflected wave arrival is influenced by the location of the predominant vascular pathological condition. If the problem affects distal small-sized vessels wave reflections will arrive later and vice versa (Castelain et al. 2001). Unfortunately, these phenomena are not easy to detect clinically. During early stages the contractile function of the overloaded right ventricle may be preserved (Stein et al. 1979), and the decreased efficiency may not be detected with routine RV function assessment methods. PVR and pulmonary artery pressure are insufficient for the evaluation of all the forces that oppose RV ejection. Nevertheless, pulmonary wave reflections have been documented in patients with primary and thromboembolic pulmonary hypertension by time domain analysis of the pulmonary artery pressure waveform (Castelain et al. 2001), but have not been studied in ARDS patients. A visible notching on the systolic portion of the pressure wave form indicates the site of the reflected wave arrival and the pressure increase above the notching is an indication of the magnitude of the reflected wave.

We have recently evaluated the wave reflection phenomena by time domain analysis of the pulmonary arterial waveform in an experimental porcine model of ARDS (Oviedo et al. 2013). We hypothesised that the lung condition could dynamically modulate wave reflection phenomena, and found that lung collapse

increased the magnitude of wave reflections which arrived during mid-systole. When collapse was minimised, reflected waves decreased and arrived later in the systolic phase, even at similar levels of pulmonary artery pressure.

Towards a More Integrative Protective Ventilation Approach

The pathophysiological aspects of heart-lung interactions discussed could help in introducing additional interventions to confer improved protection to the functional unit as a whole that is the lung, the pulmonary circulation and the RV. Given the importance of lung volume these interventions should be aimed at restoring and maintaining end-expiratory lung volume. A lung recruitment manoeuvre, when effectively performed, can restore lung volume by re-expanding collapsed lung regions. This results in a more homogenous distribution of tidal volume that is redistributed to more dependent lung regions, eventually decompressing non-dependent hyperinflated regions (Borges et al. 2006). In addition, by increasing the gas exchange area, recruitment improves oxygenation and carbon dioxide elimination, which can diminish the pulmonary vascular tone by reducing hypoxic pulmonary vasoconstriction. An expanded lung could also reduce the presence and effects of wave reflection phenomena and thus RV efficiency by two potential mechanisms: capillary recruitment and a decrease in pulmonary arterial elastance. The restored lung volume is then maintained by an individualised level of PEEP. Clinically this individualised PEEP level can be identified by means of a decremental PEEP trial after recruitment, searching for the level resulting in maximal lung compliance (Suarez Sipmann et al. 2007). Ideally this level should provide an optimal balance between minimal lung collapse and overdistension and would correspond to the lowest point of the PVR-lung volume curve. Furthermore, best compliance results in the lowest driving pressure for a given tidal volume that would then be adjusted to the size of the functional lung (Amato et al. 2015). Once the lung is stabilised with the individualised PEEP level, tidal volume and plateau pressure should be maintained as low as possible. The RV unloading effect of lung recruitment and PEEP has been described in cardiac surgery patients (Miranda et al. 2006). A recruitment effect may also account for the RV unloading of ARDS patients ventilated in the prone position (Vieillard-Baron et al. 2007).

Conclusion

The components of the functional unit interact in a complex manner. Mechanical ventilation and the lung condition have an important modulation role in this interaction. Pulmonary vascular dysfunction frequently complicates the course of ARDS and negatively affects patient's outcome. Implementing a protective ventilatory strategy extended to the lung, the pulmonary circulation and the right ventricle should constitute an early target during mechanical ventilation in ARDS patients. Such a ventilation strategy should aim at restoring and maintaining lung volumes by means of recruitment and individualised PEEP selection in combination with a strict limitation of tidal volume and inspiratory pressures. An improved understanding of pulmonary vascular haemodynamics and its response to mechanical ventilation will help in further refinements of global protective strategies. Summarising, protective ventilation should be good for both lung and the heart! ■

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FLUID RESUSCITATION IN BURNS

WHAT IS NEW?

The understanding of burn shock pathophysiology and subsequent development of fluid resuscitation strategies have led to dramatic outcome improvements in burn care during the last decades. However, while under-resuscitation has become rare in clinical practice, there is growing concern that over-resuscitation, leading to increased morbidity and mortality, has become more and more common in burn care. In this article, current evidence regarding the available resuscitation fluids is discussed as well as the endpoints that can be used to guide fluid resuscitation.

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Following a severe burn injury, an overwhelming systemic inflammatory response with capillary leak syndrome is initiated, resulting in a combined hypovolaemic and septic shock (Malbrain et al. 2014a). Numerous articles regarding burn resuscitation have been published over the last decades; however, there is no universal consensus on how to achieve adequate resuscitation whilst avoiding the adverse effects of excessive resuscitation. As a consequence, a dynamic fluid protocol including also active de-resuscitation is needed (Cordemans et al. 2012a; Cordemans et al. 2012b; Kushimoto et al. 2012; Kirkpatrick et al. 2013).

Historical Background

Although burn wounds and burn-related deaths have been part of human history, fluid resuscitation management is relatively new, dating back less than a century. In 1921, landmark research was performed by Frank Underhill following the New Haven Rialto Theater fire (Underhill 1930). Following the Coconut Grove fire in 1942, Cope and Moore stated in a series of articles on thermal injury that wound oedema contributed to the burn shock, and the proposed volume for resuscitation was based on the patient's body weight and the severity of the burn, the so-called "body weight burn budget" (Cope and Moore 1947). In 1952 Evans postulated a formula for fluid volumes based on total burned surface area (TBSA) and also introduced colloids in burn resuscitation (Evans et al. 1952). This formula would become the standard until the 1960s (Haynes et al. 1955). At that time Baxter and Shires developed their pivotal formula at the Parkland Memorial Hospital, which has lasted decades as the gold standard for fluid resuscitation in acute burn care across the world (Baxter and Shires 1968). The formula advocates 4ml crystalloids per kg per % of TBSA per 24h, of which half is given during the first eight hours (Baxter and Shires 1968). Resuscitation fluids are guided by diuresis (target 1 ml/kg/hour) and increased with steps of 25%. During the second 24 hours of resuscitation, colloids are allowed, and resuscitation volume is adapted according to diuresis (with a gradual decrease if diuresis is adequate).

Fluid Creep

Over the last 15 years, however, multiple centres have reported excess fluid administration (Cartotto and Zhou 2010; Faraklas et al. 2012; Saffle 2007; Shah et al. 2003; Strang et al. 2014). This fluid excess often leads to "resuscitation morbidity", a group of complications linked to fluid overload, such as pulmonary oedema (due to capillary leak and increased extravascular lung water), delayed wound healing, delayed recovery of gastrointestinal function (with ileus), limb compartment syndrome, orbital compartment syndrome, intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) leading to multiple organ failure (Malbrain et al. 2014a; Kirkpatrick et al. 2013; Malbrain et al. 2014b; Pruitt 2000; Sullivan et al. 2006; Ball et al. 2006).

This discrepancy between the predicted and the administered fluid is known as "fluid creep", a term brought to life by Basil Pruitt (2000). There are different hypotheses regarding the phenomenon, although its cause remains uncertain. One interesting hypothesis is that of "opioid creep", a term introduced by Sullivan et al. (2004).

Over the last fifteen years, a lot of attention has been paid to the phenomenon of fluid creep, and the awareness of morbidity caused by resuscitation has grown significantly. Efforts should therefore be made to avoid "futile loading" with excessive amounts of crystalloids and the role of colloids in early resuscitation needs to be further investigated (Lawrence et al. 2010).

Recommendations for fluid resuscitation, resuscitation endpoints and suggestions for treatment algorithms are listed in Table 1.

Types of Resuscitation Fluid

Crystalloids

Crystalloids are aqueous solutions of mineral salts, which are freely permeable across membranes. In 1882 a "normal" saline solution (NaCl 0.9%, 154 mEq/L) was developed by Hamburger, believing it was the sodium concentration of the plasma (Awad et al. 2008). The most well-known adverse effect is hyperchloremic metabolic acidosis after infusion of large volumes saline and, as such, **normal saline** cannot be recommended as resuscitation fluid in severe burns (Stephens and Mythen 2000). The "balanced" or "physiologic" solutions such as lactated Ringer's, Hartmann's solution or Plasmalyte add the anion bicarbonate in the form of lactate,

acetate or gluconate; it provides a strong ion difference which is feasible from an acid-base perspective (Van Regenmortel et al. 2014; McDermid et al. 2014; Young et al. 2014). From the beginning of burn resuscitation until present, most resuscitation formulas advocate the use of **balanced crystalloid solutions** and as such they are a pragmatic initial choice in severe burns patients. One observational study reported lower Sequential Organ Failure (SOFA) scores in severely burned patients resuscitated with Ringer's acetate (Gille et al. 2014).

Colloids

Specifically in burn resuscitation, the use of colloids in the first 24 hours has been controversial since it was thought that the existing capillary leak would allow large molecules to leak into the extravascular space and exert an osmotic pull increasing the formation of oedema (Baxter 1974). During the last decades colloids have been omitted from many resuscitation formulas. In the last fifteen years however, renewed interest in colloids has arisen, instigated by the awareness of morbidity related to resuscitation and fluid creep. Until recently, the low molecular weight hydroxyethyl starch (HES) solutions were widely used as a resuscitation fluid in critically ill ICU, surgical and burn patients. However, recent trials such as Crystalloid versus Hydroxyethyl Starch Trial (CHEST), Scandinavian Starch for Severe Sepsis/Septic Shock (6S) and Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients With Severe Sepsis (CRYSTMAS) showing increased mortality and higher rate of renal replacement therapy have raised alarming conclusions regarding the safety of HES solutions (Myburgh et al. 2012; Perner et al. 2012; Guidet et al. 2012). This led to the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) **against the use of HES solutions** in patients with sepsis, burn injuries or critically ill patients, because of increased kidney injury and mortality (Coriat et al. 2014).

Albumin

Albumin is a natural plasma protein that contributes most to intravascular oncotic pressure in humans. The most common solution is 4 or 5% albumin in saline. It is a relatively expensive solution and its availability may be limited in some countries. Although albumin resuscitation has been used with some reservation, especially in the acute phase of burn resuscitation, trials provide promising data regarding the use of albumin as an adjunctive in burn resuscitation (Lawrence et al. 2010; Cochran et al. 2007).

Table 1. Recommendations Regarding Fluid Resuscitation and Resuscitation Endpoints in Severe Burns Patients

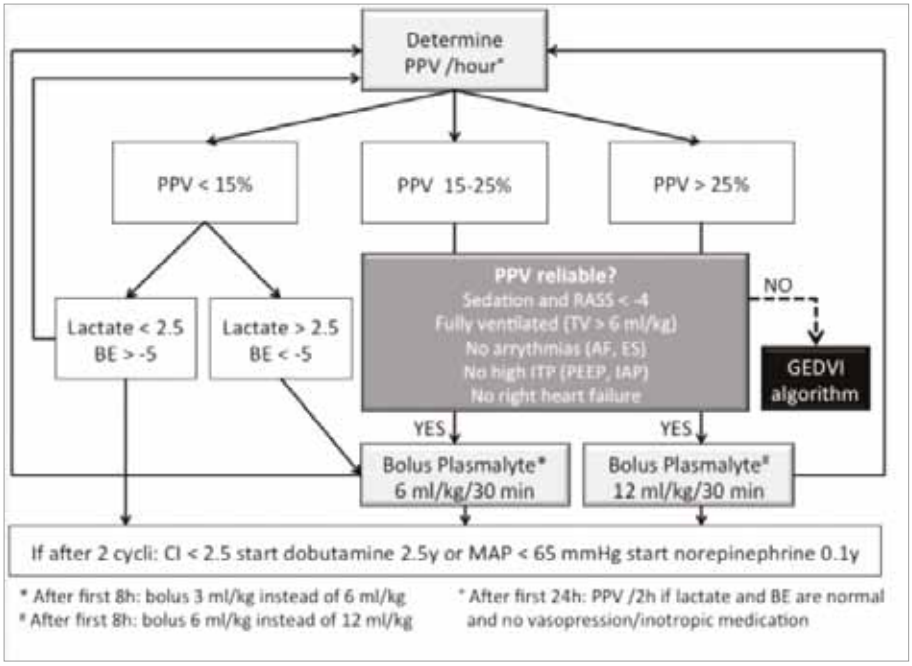
Fluids	
1. Normal saline	Given the fact that fluid resuscitation in burn management requires large volumes, the use of saline cannot be recommended in a burn resuscitation protocol.
2. Balanced crystalloid	Based on the available evidence, balanced crystalloid solutions are a pragmatic initial resuscitation fluid in the majority of acutely ill (and burn) patients.
3. Semi-synthetic colloids	Given the recent data concerning the use of semi-synthetic colloids (and starches in particular), their use in critically ill patients, including burn patients, cannot be recommended.
4. Albumin	Based on the available evidence the use of albumin 20% can be recommended in severe burns, especially in the de-resuscitation phase guided by indices of capillary leak, body weight, (cumulative) fluid balance, fluid overload, extravascular lung water and IAP.
5. Hypertonic solutions	To this day, there is insufficient evidence to reach consensus regarding the safety of hypertonic saline in burn resuscitation. Whenever using hypertonic saline in clinical practice however, close monitoring of sodium levels is highly advised.
Adjunctive Therapy	
6. Vitamin C	Given the available evidence, the benefit of adjunctive high dose ascorbic acid treatment can be highly suspected to limit fluid intake and to prevent secondary abdominal hypertension; and equally important, no adverse effects have been reported.
7. Plasmapheresis	The benefit of plasmapheresis on outcome in burn patients still needs to be validated in large prospective, randomised trials. As such its use cannot be recommended.
8. Intravenous imunoglobulins (IVIG)	The use of IVIG should be limited to cases of toxic epidermal necrolysis.
Abdominal Hypertension	
9. Intra-abdominal pressure (IAP)	During the resuscitation phase as well as the recovery phase intra-abdominal pressure (IAP) needs to be measured in burn patients at least 4 to 6 times per day.
10. Medical treatment	Medical management (improvement of abdominal compliance, evacuation of intra-abdominal contents, evacuation of intra-luminal contents, limitation of fluid intake, optimisation of organ perfusion) comes first, and should be initiated whenever IAP increases above 12 mmHg.
11. Surgical treatment	Escharotomies should be performed in case of circular thoracic or abdominal eschars. Surgical decompressive laparotomy is only a last resort in case medical management fails.
Resuscitation Endpoints	
12. Monitoring	Every severely burned patient (> 20% TBSA in adults or > 15% TBSA in children) should be adequately monitored with regard to fluid status, fluid responsiveness and organ perfusion.
13. Urine output	Diuresis is a poor endpoint that may lead to over- or under- estimation of fluid resuscitation and as such can no longer be recommended. However, in situations with limited monitoring techniques it can still be used to guide fluid resuscitation (See urine output algorithm).
14. Barometric preload	Barometric preload indicators like central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) should not be used to guide fluid resuscitation in burn patients.
15. Volumetric preload	Volumetric preload indicators (like right ventricular or global end-diastolic volume) are superior compared to barometric ones and are recommended to guide fluid resuscitation, especially in burn patients with increased IAP. (See GEDVI algorithm).
16. Lung water	The use of extravascular lung water is recommended to guide de-resuscitation in burn patients not transgressing spontaneously from Ebb to Flow phase.
17. Fluid responsiveness	Fluid resuscitation in burn patients should be guided by physiological parameters or tests that are able to predict fluid responsiveness. (See PPV algorithm).
18. Perfusion	Fluid resuscitation should only be given/increased in case of evidence of tissue hypoperfusion (base deficit, lactate, etc. ....).
Stepwise approach	
19. PPV Algorithm	If a patient is sedated and mechanically ventilated, an algorithm based on pulse pressure variation (PPV) can be used in severe burns, under the condition that PPV measurements are reliable (see Figure 1).
20. GEDVI algorithm	If PPV is unreliable, volumetric parameters obtained with transpulmonary thermodilution can be used to guide fluid resuscitation in severe burns. Here, the GEDVI is interpreted as a measure of preload and EVLWI as a safety parameter warning for pending pulmonary oedema (see Figure 2). If the GEDVI is high, the measurement needs to be corrected with the global ejection fraction as this leads to a more accurate estimation of preload.
21. Urine output algorithm	If PPV or volumetric parameters are unreliable, or when monitoring possibilities are limited, urine output can be used to guide fluid resuscitation in severe burns

CVP: central venous pressure
EVLWI: extravascular lung water index
GEDVI: global end-diastolic volume index
IAP: intra-abdominal pressure
IVIG: intravenous immunoglobulins
PAOP: pulmonary artery occlusion pressure
TBSA: total burned surface area

Table 2. Global Ejection Fraction Corrected Volumetric Target Values

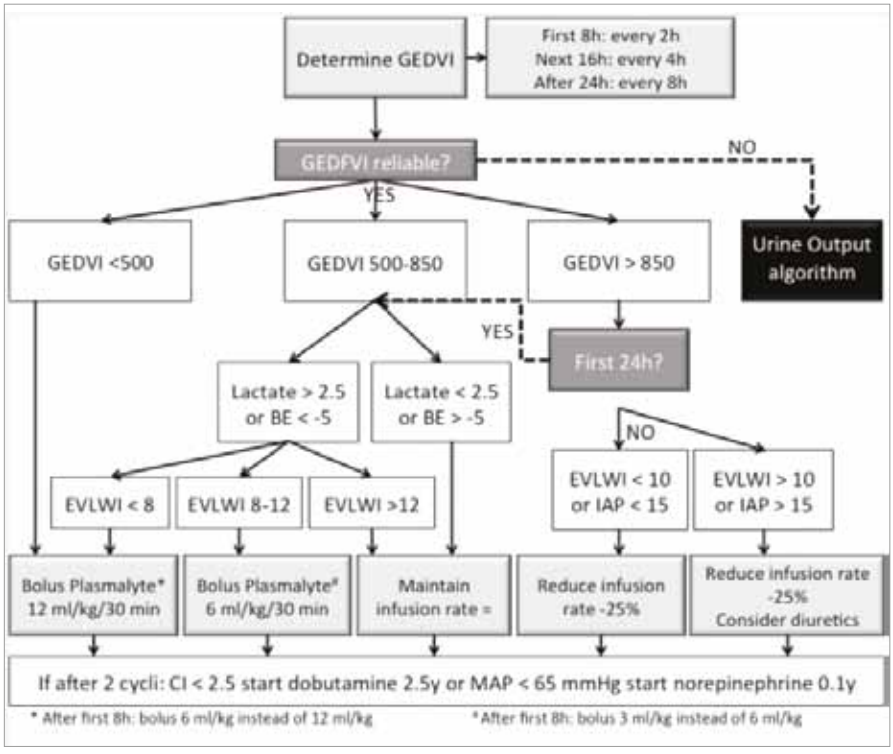
Ejection Fraction	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%
GEDVI-target (normal)	1175	1050	950	850	775	700	625	575	525	475	435
GEDVI-target (critically ill)	1450	1300	1150	1025	925	825	750	675	600	550	500

GEDVI global end-diastolic volume index, **(normal)** refers to a stable patient, **(critically ill)** refers to an unstable patient with clinical diminished preload



AF: atrial fibrillation
BE: base excess
CI: cardiac index
ES: extrasystole
GEDVI: global end-diastolic volume index
IAP: intra-abdominal pressure
ITP: intrathoracic pressure
MAP: mean arterial pressure
PEEP: positive end-expiratory pressure
PPV: pulse pressure variation
TV: tidal volume

Figure 1. Pulse pressure variation algorithm to guide resuscitation in severely burned patients. If the patient is mechanically ventilated and PPV is reliable fluid resuscitation is guided by the PPV algorithm.



BE: base excess
CI: cardiac index
EVLWI: extravascular lung water index
GEDVI: global end-diastolic volume index
IAP: intra-abdominal pressure
MAP: mean arterial pressure

Figure 2. Global end-diastolic volume index algorithm to guide resuscitation in severely burned patients. If PPV is unreliable and the patient has a PiCCO catheter and GEDVI is not reliable fluid resuscitation is guided by the GEDVI algorithm.

Hypertonic saline

Hypertonic saline has been used for decades in burn resuscitation; theoretically, it expands the circulating volume by an intravascular water shift (Duchesne et al. 2015). This will decrease tissue oedema and lower the rate of complications claimed by proponents. In the 1970s, studies concluded that hypertonic saline indeed reduces the volume needed for burn resuscitation (Monafo et al. 1973; Moylan et al. 1973).

Adjunctive Therapy

Vitamin C

In the 1990s, Matsuda et al. were able to reduce fluid requirements and oedema formation during burn resuscitation in dogs and guinea pigs using high-dose ascorbic acid treatment (Matsuda et al. 1991; Matsuda et al. 1992). A few years later they reproduced in a prospective, randomised study the proposed beneficial effects of high dose ascorbic acid in humans (Tanaka et al. 2000).

Plasmapheresis

In the 1980s a retrospective study described plasmapheresis treatment in patients who failed to respond to conventional therapy. This therapeutic response was characterised by a sharp decrease in fluid requirements from a mean of 260% above the predicted hourly volume to within calculated requirements by 2.3 hours following plasma exchange (Warden et al. 1983).

Role of Abdominal Hypertension

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are major complications in burn patients leading to multi-organ dysfunction and death, requiring specific strategies to prevent, monitor, diagnose and treat these complications (Malbrain et al. 2015). In 1994 it was reported that the incidence of ACS was linked with the extent of burn injury. This relationship between TBSA and development of ACS was confirmed in other studies (Strang et al. 2014; Oda et al. 2006; Ivy et al. 2000; Kirkpatrick et al. 2009). Typically, ACS occurs when TBSA is greater than 60%; however, patients with a lower TBSA may also develop IAH/ACS (Oda et al. 2006). Whether the development of IAH and ACS is iatrogenic or can be avoided is not clear. In 2000 Ivy stated that a volume administration of > 250ml/kg in the first 24 hours is a risk factor for ACS; this fluid quantity is known as the Ivy index (Ivy et al. 2000).

Resuscitation Targets and Endpoints

When resuscitating burn patients, clinicians need to evaluate the optimal amount of fluid to be given. The clinical interpretation of haemodynamic status can be very difficult in burn patients, which is problematic because there is a risk for inadequate organ perfusion as well as a risk of over-resuscitation.

Urine Output

Urine output has classically been the primary endpoint to guide resuscitation in burn care; popular opinion was that a target diuresis of 0.5ml/kg/h in adults and 1ml/kg/h in a paediatric population should be pursued. This endpoint, however, has been doubted in studies. In a retrospective review (Dries and Waxman 1991), there was no correlation between urine output and invasively derived physiologic variables; moreover urine output was unable to identify fluid responders after a fluid challenge. Other studies also suggest the inconsistency of urine output as a resuscitation target (Shah et al. 2003; Pruitt 2000), perhaps even contributing to the phenomenon of fluid creep.

Barometric Preload

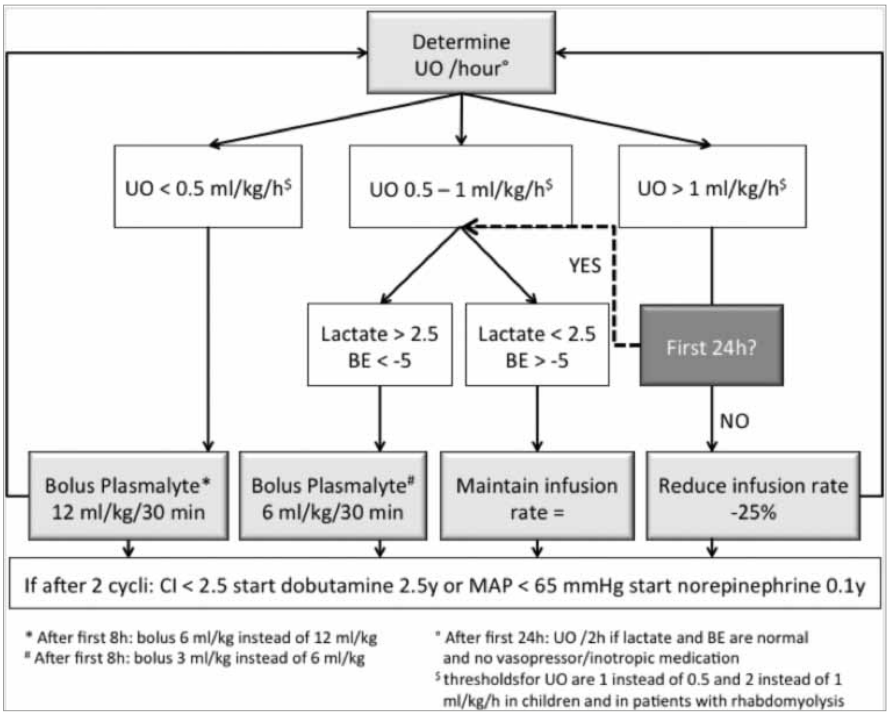
Studies in recent years have questioned the efficacy of pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP), as endpoints for resuscitation, as these parameters do not correlate with ventricular filling pressures and ventricular end-diastolic volumes (Marik 2011; Michard and Teboul 2002). In a systematic review, Marik found a very poor relationship between CVP and blood volume, as well as the inability to predict the haemodynamic response to a fluid challenge, making CVP and PAOP obsolete as standardised endpoints for fluid resuscitation. Its use should be reserved for specific indications (Marik et al. 2008).

Volumetric Preload

Advances in technology such as transpulmonary thermodilution allow the monitoring of preload in static volumetric indices such as global end-diastolic volume (GEDV) and extravascular lung water (EVLW). Numerous studies have shown that these volumetric indices represent preload more precisely in comparison to urine output (Csontos et al. 2008; Sanchez et al. 2013) or cardiac filling pressures (Lichtwarck-Aschoff et al. 1996; Malbrain et al. 2010), where during the early resuscitation phase, hypovolaemia might not be reflected by blood pressure or urine output (Sanchez et al. 2013). Correcting these volumetric preload parameters by measures of ejection fraction, this further improves the ability of these parameters to assess changes in preload over time as presented in Table 2 (Malbrain et al. 2010). The EVLW together with the pulmonary vascular permeability index (PVPI) can be used to determine the presence of lung oedema, which can be very useful as a safety parameter during resuscitation (Sanchez et al. 2013), in patients with inhalation injury or in guiding fluid de-resuscitation if a patient fails to proceed to the "flow" phase (Sanchez et al. 2014a; Cordemans et al. 2012a; Cordemans et al. 2012b).

Fluid Responsiveness

To determine the benefit of fluid administration, several clinical and haemodynamic tests can be used. As mentioned above, CVP does not



BE: base excess
CI: cardiac index
IAP: intra-abdominal pressure
MAP: mean arterial pressure
UO: urine output

Figure 3. Urine output algorithm to guide resuscitation in severely burned patients. If the patient has no PiCCO catheter (or GEDVI is not reliable) and PPV is not reliable, fluid resuscitation is guided by the UO algorithm.

predict fluid responsiveness (Michard and Teboul 2002; Marik et al. 2008), but studies have shown that dynamic parameters, obtained by invasive arterial monitoring and pulse contour analysis, such as pulse pressure variation (PPV) and stroke volume variation (SVV) are highly predictive of fluid responsiveness (Marik et al. 2009) in mechanically ventilated patients.

Holistic Approach: Introduction of a New Protocol

In an attempt to effectively guide fluid resuscitation in burn patients in the future, whilst avoiding deleterious effects of over-resuscitation, a multimodal protocol using a modified formula and multiple endpoints is suggested.

Fluid resuscitation is initiated in adults with >20% TBSA and children with >15% TBSA. A modified Parkland formula is suggested; a balanced crystalloid is given at 2 ml/kg/%TBSA in the first 24 hours in combination with albumin 20% at 0.2 ml/kg/%TBSA; half of the total dose of crystalloids and colloids is given in the first eight hours, the other half between 8-24 hours. During the next 24 hours a calcium-free balanced salt solution is given at 0.75 ml/kg /%TBSA in combination with albumin 20% at 0.075 ml/kg /%TBSA. These resuscitation rates are fixed, and fluids are gradually decreased after the first 24 hours of burn shock resuscitation. Throughout the resuscitation, basic fluid needs are supplemented in the form of a glucose containing solution at 30ml/kg/24h; enteral nutrition, if given, is subtracted from this basic fluid administration total. Fluids are changed or adapted throughout resuscitation according to biochemical analysis (base excess (BE), lactate, etc.) and concomitant medical conditions (see algorithms as discussed further). During the first 24 hours, resuscitation fluids as calculated above are kept at constant rate and when needed fluid boluses can be given. De-resuscitation (with gradual decrease in resuscitation fluids) is only started after the first 24 hours. Extra albumin 20% can be administered based on serum levels of albumin (target 30 g/L) or colloid oncotic pressure (COP, target 16-18 mmHg).

PPV Algorithm

Different endpoints in combination with lactate and BE can be used in order to guide fluid resuscitation. If a patient is sedated and mechanically ventilated, PPV is used, whenever reliable. The subsequent PPV algorithm is presented in Figure 1; however, the clinician needs to check whether the patient has conditions leading to incorrect interpretation of PPV (Hofkens et al. 2015).

GEDVI Algorithm

If PPV is unreliable, volumetric parameters are measured with the use of transpulmonary thermodilution. Here the GEDVI is interpreted as a measure of preload and EVLWI as a safety parameter warning for pending pulmonary oedema. The subsequent GEDVI algorithm is presented in Figure 2. Correct interpretation of volumetric parameters needs to be done in relation to the presence or not of other conditions (like valvulopathy, catheter position, extracorporeal circuit, etc.) (Hofkens et al. 2015).

Urine Output Algorithm

If PPV or volumetric parameters are unreliable, or when monitoring possibilities are limited; urine output (UO) can be used to guide fluid resuscitation. The subsequent UO algorithm is presented in Figure 3. The importance of measuring IAP needs to be underlined when using urine output as a resuscitation target, as IAH and ACS decrease urine output.

Conclusions

Burn resuscitation keeps evolving and new trends develop. Over the last fifteen years, much attention was given to avoid over-resuscitation and subsequent morbidity and mortality; fluid creep is recognised by nearly all physicians involved in burn care.

Efforts should be made to avoid excess crystalloid administration by re-thinking resuscitation protocols. Evidence suggests that the addition of a colloid such as albumin 20% may decrease fluid requirements, and may potentially reduce resuscitation-related morbidity; however, the use of colloids in burn resuscitation continues to be a great source of controversy and discussion.

Endpoints of burn resuscitation should be redefined. The traditional UO target does not represent preload accurately; however, barometric preload parameters also seem to lack this ability. Evidence suggests that advanced haemodynamic monitoring with pulse contour analysis (PPV) and transpulmonary thermodilution (GEDVI) may provide superior endpoints to prevent under-resuscitation, while EVLWI can be used as a safety parameter to avoid over-resuscitation and to guide the de-resuscitation process.

Acknowledgements

MLNGM is member of the medical advisory board of Pulsion Medical Systems (Maquet Getinge Group). The other authors have no possible conflicts of interest related to the content of this paper. This article is a selection of a full review paper published under the Open Access CC BY Licence in *Anaesthesiology and Intensive Therapy*.

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BENCHMARKING
LESSONS LEARNT

Benchmarking —comparing your own results with those of others—has the potential to reveal areas in which your unit could improve. However, there are pitfalls you should be aware of.

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When he was the CEO of Xerox Corporation, David T. Kearns stated, "*Quality improvement can't be measured in a meaningful way against standards of your own internal devising*" (Kearns 1990). This sentence captures the basic concept of benchmarking: unless you are willing to compare your results with those of others, your impressions of quality may be too optimistic.

Many aspects of intensive care unit (ICU) performance can be benchmarked. These include safety of care, measures of economic performance and patient and family satisfaction. This article concentrates on the challenges of comparing severity of illness-adjusted mortality figures.

Beginning of Benchmarking in Intensive Care

In the early 1980s, Knaus and co-workers presented a severity-of-illness scoring system for ICU patients, called the Acute Physiology and Chronic Health Evaluation (APACHE), and demonstrated its use in comparing patient populations from different ICUs and their outcomes (Knaus et al. 1981; 1982). Although it was developed in America, APACHE was soon implemented in other countries. Hospitals in the USA, France, Spain and Finland participated in the first multinational study using this scoring system (Wagner et al. 1984).

APACHE was soon followed by the Simplified Acute Physiology Score (SAPS), developed in France (Le Gall et al. 1983). Both systems have been developed further, resulting in several updated versions. The basic principle is similar in all versions: the patient's age, conditions at admission, comorbidity and abnormal current physiological measurements are given points to produce a score that is converted into a predicted probability of the patient dying during the actual hospitalisation. For an individual patient, the score reflects the severity of illness at the beginning of the intensive care period, but the associated probability of death is never the same as the final outcome: the probability is between 0 and 1 (but never exactly 0 or 1), whereas the outcome is either survival or death. Probabilities of death are useful as an aggregate measure of risk in a large group of patients, as the sum of individual probabilities provides the expected number of deaths (Le Gall 2005). Dividing the number of deaths that occur during a certain period by the expected number of deaths gives the standardised mortality ratio (SMR).

After these severity-of-illness scoring systems made it possible to adjust for differences in patient case mix, comparing mortality outcomes of different ICUs has become popular. Large benchmarking programmes are running in many countries. The authors of this article represent the nationwide ICU quality and benchmarking programmes in Finland (the Finnish Intensive Care Consortium, started in 1994) and Norway (the Norwegian Intensive Care Registry, since 1999).

Benchmarking: A Suitable Concept for Industrial Plants, but What About Intensive Care?

Benchmarking involves comparing the performance of one organisation to that of similar organisations, with the aim to identify best practices and best performers and learn from them. The idea originated in the manufacturing industry and is not easily applied to intensive care medicine, as ICUs work with more complex processes than simply making multiple copies of standard wares out of standard raw materials.

Even so, we believe that we can apply certain ***essential lessons*** learnt by benchmarking pioneers in the manufacturing industry to intensive care:

1. **It is dangerous to become complacent** (Kearns 1990). No matter how good your ICU is today, if you stop learning and improving, you are going to regress. Beware of self-satisfaction!
2. **If you do not document your results, it is easy to imagine** that you and your team are doing a good job. This impression may be false.
3. **Comparing your current results with your previous results** is better than not documenting them at all, but it **may not be enough**. Comparing your results with those of others may open your eyes to areas in which you could improve.
4. **Intensive care medicine is team work.** The expertise of one individual doctor or the excellence of one nursing team has little impact on the overall performance of the healthcare system. Benchmarking provides an opportunity to detect weaknesses in the treatment chain of some patient groups.

Some may argue that there is little evidence that benchmarking improves quality of care. It is true that no randomised controlled trial has demonstrated the superiority of an intensive care programme with benchmarking over one without. However, the benefits of benchmarking have been proven in other fields of medicine (Kiefe et al. 2001; Hermans et al. 2013). Generally, poor quality means there is much room for improvement, whereas it may be hard to improve high-quality processes further. It is not surprising that the impact of feedback from benchmarking seems to be larger when the baseline level of performance is low (Jamtvedt et al. 2006).

Measuring and even defining quality in intensive care is difficult. In a comparison of quality indicators (QI) within intensive care in eight countries, no single indicator was used in all countries. The most common QIs were the standardised mortality rate (in six of eight countries) and patient/family

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satisfaction (five of eight) (Flaatten 2012). Generally, documenting severity of illness and mortality figures is considered essential in an ICU benchmarking programme (Moreno et al. 2010).

Pitfalls of SMR and How to Avoid Them

Potential confounders influencing SMR calculations include properties of the model used to adjust for differences in baseline risk, factors affecting the measurement of severity of illness and the choice of mortality endpoint.

1. Performance of the Risk-Prediction Model

A risk-adjustment model often fits the population used for model development well. However, when one applies it to another patient population, its prognostic performance may be worse (Livingston et al. 2000). The model may systematically overestimate or underestimate the risk of death. The adequacy of risk estimation may also differ across different levels of risk: for example, the model may overestimate mortality in low-risk patient groups but underestimate mortality in high-risk patients. This is called poor calibration or poor fit of the model (Angus 2000). If the calibration is poor and there are major differences between ICUs in patient case mix, comparing SMRs is questionable. If ICUs are ranked according to SMRs, the choice of prognostic model may heavily affect the rank of a unit (Bakshi-Raiez et al. 2007; Kramer et al. 2015). Nonetheless, risk-adjustment models developed for intensive care perform better than models based solely on administrative data, which have also been used in ranking ICUs (Brinkman et al. 2012).

Over time, outcomes tend to improve and risk-adjustment models become outdated. If benchmarking programmes use old models, it is probable that SMRs will be low for most, if not all, ICUs. This must not be interpreted as evidence of perfection. To solve the problem of worsening prognostic performance of ageing risk-adjustment models, new models have been developed. However, even if a new model fits perfectly well, its performance will deteriorate as time passes (Moreno and Afonso 2008).

An alternative approach to creating a totally new model is customising an existing model to better fit a regional patient population. A common strategy is first-level customisation, which means that the variables in the model and their relative weights are unchanged but the equation converting the severity score to probability of death is updated. Very good prognostic performance can be achieved with a customised model (Haaland et al. 2014).

Whether a benchmarking programme should use an original risk-adjustment model or a locally customised or even locally created model depends on the choice of the reference population with which one wants to compare ICUs. With the original model, one can describe a patient population with a well-known severity score and compare the outcomes with those of an international reference population. However, if one wishes to compare ICUs within the benchmarking programme, then a well-fitting customised model is a better choice (Angus 2000; Moreno and Afonso 2008; Metnitz et al. 2009).

2. Factors Affecting the Measurement of Severity of Illness

Points are added to the severity score according to values of physiological parameters: the more abnormal a value, the higher the score. When data are missing, the values of the parameters in question are commonly presumed to be within the normal range, and no severity points are added. Thus patient groups with a lot of missing data may appear less severely ill than they actually are, and the calculated SMR may become erroneously high. Correspondingly, improving data completeness leads to a decrease in SMRs (Reinikainen et al. 2012).

Changing the frequency of measurement may affect the severity scoring: taking more samples increases the likelihood of obtaining abnormal values. This results in higher severity scores and lower SMRs because the scoring systems take into account the most extreme value from the observation period (Suistomaa et al. 2000). Automation of data collection with a clinical information system (CIS) increases the sampling rate of physiological data. In Finnish ICUs, the severity of illness-adjusted odds of death were 24% lower in 2005–2008 than in 2001–2004, but one-fifth of this computational improvement in outcomes could be explained by improvements in data completeness and automated data collection through the use of a CIS (Reinikainen et al. 2012). This phenomenon should be noted in benchmarking programmes if some ICUs use CIS technology and others do not.

The importance of data accuracy cannot be overstated (Angus 2000). Education and data quality monitoring are continuously needed to achieve and maintain correct and harmonised documentation practices.

Severity scores should reflect the severity of illness. However, the scoring systems are not able to distinguish a patient affected by a disease from a patient whose condition may be partly caused by substandard care prior to ICU admission or in the beginning of the ICU period.

3. Mortality Endpoints

Traditionally, vital status at hospital discharge has been used as an outcome measure. However, comparing hospital mortalities is problematic. Patients transferred to other hospitals are calculated as hospital survivors, yet some of these patients will die in the next hospital. Thus differences in hospital discharge practices can cause bias (Kahn et al. 2007).

In a recent study from Sweden, Rydenfelt et al. (2015) explored the effects of using 30-day mortality instead of hospital mortality as the outcome measure. Not surprisingly, 30-day mortality was higher than hospital mortality in almost all ICUs. What is newsworthy is that the magnitude of the difference between in-hospital and 30-day mortalities is not constant, and hospital discharge practices and patient case mix affect it: the difference increases with increasing age and severity of illness and also varies across diagnostic categories. The calculated SMR of an ICU may also be markedly influenced by the choice of mortality endpoint. Comparable findings have been published from the Netherlands: the choice of mortality endpoint (vital status at hospital discharge or at a fixed time point) affects the SMRs and SMR rank positions of ICUs (Brinkman et al. 2013). We recommend that, whenever possible, quality programmes stop using hospital mortality as the primary endpoint and start using fixed-time mortality. Preferably, the follow-up should be longer than 30 days (e.g., 6 or 12 months).

Because of the potential impact of these confounders, one needs caution when evaluating SMRs. However, this does not mean that SMRs are without value. Constant differences in SMRs can be interpreted as an indication that one should look more deeply into the situations in different units and try to identify the factors explaining the differences (Le Gall 2005). The explanatory factors may be unrelated to quality of care, but it is also possible that true quality differences exist.

Conclusion

Comparing results of intensive care is not without problems. An ICU leader should be aware of the potential confounders affecting SMR calculations. Nevertheless, benchmarking may help leaders identify what they want to find: areas in which there is room for improvement. In addition, it is also important to realise that striving for quality is a never-ending journey. Once more, we quote David T. Kearns: "*We're far from finished with our drive to improve… The pursuit of quality is a race with no finish line*" (Kearns 1990). ■

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INTENSIVE CARE SYSTEMS RESEARCH

INTERVIEW WITH ASSOCIATE PROFESSOR HANNAH WUNSCH

Hannah Wunsch is Associate Professor of Anesthesiology, Department of Anesthesia, University of Toronto, Canada. She is Staff Physician, Department of Critical Care Medicine, Sunnybrook Hospital; Senior Scientist, Trauma, Emergency & Critical Care Research Program, Sunnybrook Research Institute and Visiting Assistant Professor of Anesthesiology, Department of Anesthesiology, Columbia University, USA.

Your research centres on the organisation and management of critical care services. What drew you to this area?

In medical school, I was on rounds in a surgical ICU, seeing how complex the delivery of care was, and how many people worked to care for any individual patient. This intrigued me and led me to my interest in how we deliver critical care and what sort of difference that makes.

Big data about intensive care is available. Is it of sufficient quality, and are there items that are not being measured that should be?

There are always concerns about the data, such as the quality of specific codes and variables. It is tempting to assume that if the boxes have been ticked off then the data are accurately collected. We need to continue to ask about the quality of data being used for analyses. It is important to remember that there are huge risks associated with assessing and analysing these datasets, as it is always possible to draw wrong conclusions from data. There are also always more items one would like to see more available in large datasets, such as information on medications administered and processes of care in the ICU and hospital, as well as linkage of hospital data with outpatient data.

Your research has shown that some of the variation in intensive care use is independent of hospital and patient factors (Seymour et al. 2012). What are your thoughts on this?

This is a huge area for research. It is important to try to pinpoint what hospital drivers there are, and determine why variation is happening and why we are seeing these extremes in use and so on. The first step is to be aware that variation exists. You cannot do anything about it until you know that it exists, and it is usually quite eye-opening to see just how big the variation can be. There are potentially many different drivers of all the documented variation. You need to understand the system you are working in, and a lot comes down to these systems-level issues. In the US a driver of high ICU use could be as basic as the fact that hospitals are accountable for the wait time in their emergency rooms. Some hospitals may choose to admit patients to the ICU, because that's where there is a free bed. Severity of illness plummets when you do that, and you are not necessarily taking care of critically ill patients in the ICU, but the ICU will be full. On the other hand there are hospitals that have no step-down or intermediate care beds, so when a patient needs a slightly higher level of nursing care they have to be admitted to intensive care. These are examples of ways in which some hospitals may perhaps be using ICU beds in less efficient ways and are not matching patients to beds appropriately. There are many of these potential systems factors out there, and we need to get a better handle on how often these things occur, and what may be modified to make overall care safe and efficient.

You have researched ICU capacity, for example for mechanical ventilation (Wunsch et al. 2013), and have suggested the concept of a Starling Curve for intensive care, whereby extra beds may result in harm (Wunsch 2012). What are the issues with capacity?

Like anything this is a balance. One extreme would be to say that hospitals should run with massive excess capacity, because that way you ensure that no one ever has to wait for an ICU bed. For any individual that is certainly in their best interest, but it has to be balanced against the realities of costs, staffing and the system. We have to decide as a community what excess capacity is appropriate and at what cost potentially to patients. It is a little like saying that in an ideal world everybody will get a new car every year because every year cars get safer. We don't function that way as a society. We accept the fact that some people are driving cars that are a little less safe to drive then others. It's acceptable to have that increased risk.

However, where there are not enough beds we can demonstrate the specific harms that result from that situation, e.g. patients sitting in the emergency room for 24 hours on a ventilator or not having the appropriate nursing staffing for a patient while they are waiting for a bed. It is important to recognise that there are two extremes, but what constitutes the "best" balance, we will never know for sure. We should probably run ICUs with "slightly excess" capacity, but it's hard to pinpoint what that means. It is also important to recognise that Starling curves may be different for different countries, because values and societal norms are different. For example, around end-of-life care, what is expected in terms of care may be different. We cannot say that everybody is going to follow the same curve, but I think we need to keep questioning where we are in terms of provision of intensive care and what we are gaining or losing by those choices.

With the move to 'value-based' healthcare in the United States, what might the effect be on critical care?

This is anecdotal, but when I trained, and it's been only 6 years since I finished, there was almost no discussion of costs in the ICU. That has changed, and the way in which we are now teaching residents and fellows is to think not just about blanketing patients with tests and studies because they can, but to really think about what the patient needs done and how it will benefit them.

The only way that we are going to get from volume to value is when fee for service is no longer a driver in the ICU and where hospitals do not have a financial incentive to put someone in the ICU. Until that happens, unfortunately, there are strong incentives to fill ICU beds. For some of the big payers in the US, such as Medicare, there has already been a move towards bundled payments for all care.

Of the studies that you have conducted, are there any whose findings surprised you?

The one that stands out is what I call the "low hanging fruit study", a study of ICU bed availability in eight countries (Wunsch et al. 2008). We knew beforehand that there would be some variability in the provision of ICU beds, but I think we were absolutely shocked at just how massive the differences were between some countries. The study included countries in North America and Western Europe — no developing countries — but we still found very large variation. It led us to recognise just how big a driver bed availability could be in terms of who is admitted into intensive care and who is being treated in ICU beds. We also know now that countries that have even fewer healthcare resources show even bigger variation — 20 to 30-fold — in ICU beds (Austin et al. 2014).

What are the issues around follow-up for critical care patients?

Rehospitalisation has become a hot topic across medicine. In critical care, as in the rest of medicine, we are just getting a handle on how much it happens, to whom, and how we might prevent it (Hua et al. 2015). Awareness is increasing, and more studies are starting to come out trying to understand what's going on with these patients. We are not to the point of fully understanding how to prevent re-hospitalisations. However, there are interesting studies out there starting to propose what sort of things may help keep patients out of hospitals. Many of these studies are in specific high-risk groups, such as patients with heart failure, but many of the concepts are likely applicable to critically ill patients in general.

What are the most pressing issues for post-intensive care?

We have to be careful that we don't attribute all morbidity after intensive care to the experience of being critically ill. There is a fair amount of morbidity in this population before coming to the ICU, so it is important to quantify what amount of that morbidity really is additional and what was there before. For example, if a patient is admitted to the ICU and he or she has a history of depression and treatment for depression in the last year or two and they are then measured as having depression after intensive care, do we really say that we can and should be doing something to treat that in the ICU? That said, there are many patients who leave intensive care with new disabilities, problems or diagnoses, and unfortunately we are still in the dark in terms of showing that anything we do specifically is making a big difference to that. I think a priority right now is still to identify the key modifiable factors — and modifiable is the important word here. So far we don't have a lot of data on this. I am hopeful that in the next few years we will identify some of these modifiable factors and see some positive results from intervention studies.

"We still have a marketing problem in educating the general public to understand what is meant by intensive care"

How much are quality of life outcomes in the ICU patient-centred?

Qualitative research is not my area of expertise, but an important point about intensive care is that we still have a marketing problem in educating people to really understand what it is to need intensive care and to be in an ICU. This understanding is still not widespread amongst the public, certainly in the US and Canada. It's hard to talk with people in hypotheticals and to really delve into what matters for quality of life. Yet, on the flip side, many of our patients are not in a good position to express their preferences.

For those who have experienced intensive care, placing values on quality of life as well as quantity of life is something that the intensive care community has recognised is important — it is not about just mortality. I have a slide in some of my talks with a terrible mortality curve. I make the point that it describes the mortality over a short period of time for patients who are enrolled in hospice care. You expect them to die and the important question is really whether they are receiving good quality care and experiencing a better quality of death than many other people who maybe live a bit longer. It does challenge our central theory of ICU outcomes, which is the idea that lower mortality is always better. I think we are struggling as a community with how we incorporate quality of death into outcomes. For example, how do we evaluate a hospital that provides very high quality palliative care and has a higher overall mortality rate for their patients? They may be providing excellent care and this may be preferable to the care in another hospital that puts a tracheotomy and a feeding tube in many patients, and keeps them alive without having had proactive end-of-life discussions early on. Yet, this hospital may have a lower risk-adjusted mortality. It is a fascinating and really important area for research. I don't know how it is going to shake out in terms of how we try to measure the outcomes for patients, but it brings up important issues, particularly around the value of quality of death or dying.

This interview will appear in ICU Management's Autumn Issue, which has a cover story on "The Brain." What are your thoughts on neuro-critical care?

We need to ensure that we give people with brain injury the appropriate follow-up care they need. Providing good follow-up and rehabilitation options for brain-injured patients is important. Likewise providing very good palliative care and end-of-life care options for those with catastrophic brain injuries is also vital. There is very little research on palliative care specifically in the neuro-ICU, and yet this is a population who may benefit hugely from early discussion. I think this is an area where we will see an explosion of research in the next few years, as people work to figure out how to best meet the specific needs of this population at the end of life.

What research are you are engaged in currently?

My research is focused around the hospital drivers of different use of intensive care. That will be a lifetime of research! I am following up and elucidating some of those drivers to understand them better. I am looking at the hospital system and how that impacts intensive care, stepping back from the ICU as a single unit to look more fully at interactions between different units and wards, step-down units and the ICU. ■

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

CRITICAL CARE IN CANADA

INTERVIEW WITH PROFESSOR CLAUDIO MARTIN, PRESIDENT, CANADIAN CRITICAL CARE SOCIETY

Claudio M. Martin is President of the Canadian Critical Care Society. Dr. Martin is Professor in the Department of Medicine, Chair/Chief of Critical Care Western (Schulich School of Medicine and Dentistry, Western University) and Medical Director of Critical Care at London Health Sciences Centre in London, Ontario.

What is the role of the Critical Care Society of Canada and how important is it to have a voice for critical care?

The Canadian Critical Care Society (CCCS) is the national specialty society, representing adult and paediatric critical care medicine (CCM) physicians in Canada. Our mission is to promote and enhance critical care medicine in Canada. We espouse the philosophy of collaborative multidisciplinary practice to promote research, education and patient care in critical care medicine. To that end, our society is involved in CCM education in association with the Royal College of Physicians and Surgeons of Canada, and in CCM research with the Canadian Critical Care Trials Group.

What are the main challenges for critical care in Canada?

One challenge is the increasing demand for critical care (life support interventions) associated with a growing elderly and frail population. Meeting that demand together with appropriate end-of-life planning and decision making requires an investment in resources and public engagement. The CCCS produced a position paper in the 1990s on the subject of withholding and withdrawing life support. This position paper is being updated taking into account more recent legal decisions in Canada. We don't support that age by itself should be a determining factor for admission to critical care units.

Canada is a large and geographically diverse country. It is hard to imagine that patients in remote communities have access or receive the same level of critical care when faced with progressive and life-threatening illness compared to those in the urban centres. Some tele-ICU has been introduced in remote communities, but further work on the model and process is required. The business model that has largely supported the growth in the US does not apply in the Canadian system, and therefore tele-ICUs have not gained a major foothold in Canada.

Statistics

Total population	35,182,000
Gross national income per capita (PPP international $)	42
Life expectancy at birth m/f (years)	80/84
Probability of dying between 15 and 60 years m/f (per 1,000 population)	81/52
Total expenditure on health per capita (Intl $)	4,759
Total expenditure on health as % of GDP	10.9

Source: World Health Organization http://www.who.int/countries/can/en/ Statistics are for 2013.

Directory

Canadian Critical Care Society http://www.canadiancriticalcare.org

Canadian Association of Critical Care Nurses http://www.caccn.ca

Canadian Cardiovascular Critical Care Society http://www.cancaresociety.com

Canadian Association of Emergency Physicians http://caep.ca

Canadian Anesthesiologists' Society https://www.cas.ca/English/Home.aspx

A recent study on critical care capacity in Canada found substantial provincial variability (Fowler et al. 2015), and recommended further sharing and deployment of resources. What steps are being taken on this?

Healthcare is organised at the provincial level in Canada, although there are basic requirements and funding set out by the federal government. Some provinces, such as Ontario, British Columbia and Alberta have established system-level processes to help deal with unpredictable events to some extent. Mostly, these have been developed, tested and implemented to deal with individual patients or small numbers. Even knowing what resources are available and where they exist was progress, but it needs to be kept up-to-date. The CCCS is working to create and maintain a contact list of critical care units nationally to support this.

We are planning to do a physician manpower survey across Canada that will include some fundamental data such as bed numbers and ventilation capacity. There are also projects underway to develop provincial and national quality indicators that will allow us to better understand the availability and use of critical care beds.

What can other countries learn from critical care in Canada?

Canada has a rich history in critical care, with specialisation and advanced training for physicians, nurses, respiratory therapists and other healthcare professionals. We had visionary leaders both in education and research who promoted the field of critical care. Our Canadian culture of collaboration and compromise resulted in some early success that fostered the growth and training of young educators and researchers. ■

References

Fowler RA, Abdelmalik P, Wood G et al. (2015) Critical care capacity in Canada: results of a national cross-sectional study. Crit Care, 19: 133.

AGENDA

OCTOBER

24-28
ANESTHESIOLOGY® 2015 Annual Meeting
San Diego, USA
www.asahq.org

25-26
ISF: 14th Colloquium: Precision Medicine in Sepsis
Toronto, Canada
http://internationalsepsisforum.com/colloquium/

29-31
40th ANZICS/ACCCN ASM
Auckland, New Zealand
www.intensivecare.org.nz

NOVEMBER

4-7
4th Euro-Asian Critical Care Meeting
Ankara, Turkey
www.yogunbakim2015.org/eng

5-6
Actualité en réanimation: Réanimation, Surveillence continues et Urgences graves
Lyon, France
www.jivd-france.com

13-14
ESA Focus Meeting on Perioperative Medicine: The Cardiac Patient
Nice, France
www.esahq.org/congresses/focus-meeting-2015

17-19
Echocardiography for Hemodynamic Monitoring 2015
Brussels, Belgium
www.intensive.org

19-20
Athena International Conference: Approaching the Severely Infected Patient
Athens, Greece
www.athenaconference.com

26-28
5th International Fluid Academy Days
Antwerp, Belgium
www.imerit.org/ifad

DECEMBER

1-3
21st Postgraduate Refresher Course on "Cardiovascular and Respiratory Physiology Applied to Intensive Care Medicine"
Brussels, Belgium
www.intensive.org

7-9
State of the Art Meeting
London, United Kingdom
www.ics.ac.uk

13-16
Update on IV fluids
Rome, Italy
www.intensive.org

IN OUR NEXT ISSUE

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Egypt

ICU Management is the Official Management and Practice Journal of the International Symposium on Intensive Care and Emergency Medicine

ICU MANAGEMENT IS PUBLISHED BY
MindBYTE Communications Ltd
9, Vassili Michailidi CY-3026 Limassol, Cyprus
E-mail: office@icu-management.org
Website: www.icu-management.org

PUBLISHER
MindByte Communications Ltd — office@icu-management.org

MEDIA CONTACT, MARKETING, ADVERTISING
Katya Mitreva — k.m@icu-management.org

SUBSCRIPTION RATES
One year — 55 Euros + 5% VAT if applicable
Two years — 90 Euros + 5% VAT if applicable

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

ART DIRECTOR
Marilena Patatini — art1@mindbyte.eu

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

REFERENCES
References cited in this journal are provided to ICU Management by the authors and are available on request at editorial@icu-management.org.

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according to the standards of International Business Press Audits.

ICU Management is independently audited on behalf of ISICEM by AKC