ICU
MANAGEMENT & PRACTICE
VOLUME 17 - ISSUE 3 - AUTUMN 2017

CSL Behring
Supplement from Euroanaesthesia 2017 Symposium

Recovery

The role of autophagy in the metabolism and outcomes after surgery, *J. Gunst et al.*

Fast-track surgery: a multidisciplinary collaboration, *H. Kehlet*

The patient voice in Enhanced Recovery After Surgery, *A. Balfour & R. Alldridge*

The role of physiotherapy in Enhanced Recovery after Surgery in the ICU, *T.W. Wainwright et al.*

Innovations in monitoring: from smartphones to wearables, *F. Michard*

Physical rehabilitation in the ICU: understanding the evidence, *C. M. Goodson et al.*

Optimising nutrition for recovery after ICU, *P.E. Wischmeyer*

Outcomes after 1 week of mechanical ventilation for patients and families, *M. Parotto & M.S. Herridge*

Continuing rehabilitation after intensive care unit discharge, *S. Evans et al.*

The hidden faces of sepsis, what do they tell us? *I. Nutma-Bade*

PLUS

Ultrasound-guided mechanical ventilation, *F. Mojoli & S. Mongodi*

Haemodynamic monitoring: stuff we never talk about, *C. Boerma*

Animal-assisted activity in the intensive care unit, *M.M. Hosey et al.*

From command and control to modern approaches to leadership, *T. Dorman*

Enabling machine learning in critical care, *T.J. Pollard & L.A. Celi*

09
9 771377 756005

You are Cordially Invited to Our Scientific Symposium at ESICM LIVES 2017 in Vienna

Caring for the Critically Ill Patient: Novel Strategies to Optimize Oxygenation and Oxygen Delivery (DO_2)

Location: Room Glasgow, ACV – Vienna, Austria

Date and Time: **Monday September 25th • 12:30 - 14:00**
Lunch will be provided

Chairperson: **Prof. Azriel Perel, MD**

Please register at www.masimo.com/TheFuture

Space is Limited RSVP Required

Presenters

The Role of Noninvasive Assessment of Fluid Responsiveness: New Frontiers

Jean-Louis Teboul, MD, PhD
Professor of Therapeutics and Intensive Care Medicine
Hospital CHU Bicêtre, Department of Intensive Care
University Hospital and School of Medicine Paris-Sud
Le Kremlin Bicêtre, Paris, France

Oxygen Delivery in Acutely Ill Patients: How Much, When & Where Does It Go

Luciano Gattinoni, MD
Professor of Anesthesiology and Intensive Care, Guest Professor at the Department of Anesthesia II
Zentrum Anaesthesiologie Rettungs und Intensivmedizin Universität Klinikum Goettingen
Goettingen, Germany

The Importance of Individualized Oxygen Therapy: Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke

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

Obese Patients and Reduced Pulmonary Reserve: Challenges & Insights Improving Patient Safety

Daniel A. Reuter, MD, PhD
Professor of Anesthesiology
Vice Chair Department of Anesthesiology
Center of Anesthesiology and Intensive Care Medicine, Hamburg-Eppendorf
University Medical Center, Hamburg
Hamburg, Germany

Iatrogenic Hemodilution: A Possible Cause for Avoidable Blood Transfusions?

Azriel Perel, MD
Professor of Anesthesiology and Intensive Care
Sheba Medical Center, Tel Aviv University
Tel Aviv, Israel

ESICM LIVES 2017

Masimo

PLCO-001235/PLLT-10555A-0817

Interactive Session, please ask any questions to our Faculty now! For more information, please stop by Masimo, Stand #511. Register and ask your questions at www.masimo.com/TheFuture

GE Healthcare

BOOTH #704

Monday
September 25th

12:30 - 14:00
ROOM AMSTERDAM

SYMPOSIUM

How to enhance clinical decision support in the ICU?

Chairman: *Prof. Diederik GOMMERS (ERASMUS University, Rotterdam)*
Co-chairman: *Prof. Antoine VIEILLARD BARON (Hôp. Ambroise Paré, France)*

- **Impact of user interface design on patient safety**
  Prof. Erwan L'HER *(CHRU de Brest, France)*
- **Ultrasound-guided assessment in mechanical ventilation**
  Prof. Francesco MOJOLI *(University of Pavia, Italy)*
- **Transforming hemodynamic management in the critically ill? Ultrasound!**
  Prof. Mervyn SINGER *(UCL London, United Kingdom)*
- **From clinical decision to predictive analytics in the ICU**
  Prof. Jean-Daniel CHICHE *(Hôpital Cochin, France)*

Recovery

Recovery after critical illness has received increasing attention in recent years, and rightly so. We highlighted neglect of recovery as one of the ten big mistakes in intensive care medicine (Vincent et al. 2014). While survival has improved tremendously, for a long time insufficient attention was given to how patients (and their families and caregivers) were coping after leaving the ICU. Planning for recovery is important even before the ICU, in scheduling surgery and perioperative care, and during and after the ICU stay. Enhanced recovery after surgery (ERAS) is now a feature of many different surgeries. Even for more complex operations that include planned ICU admission, the recovery pathway is part of the planning.

Our cover story begins with autophagy. Jan Gunst, Ilse Vanhorebeek and Greet Van den Berghe consider the role of autophagy in recovering from organ failure and muscle weakness. They note the potential for targeting autophagy by activating it pharmacologically or modulating it via metabolic interventions. Next, the "father" of fast-track surgery, Henrik Kehlet, shares his reflections on the progress of fast-track surgery worldwide, the need for multidisciplinary teamwork in optimising perioperative care, and the importance of patient and family information. The patient perspective on enhanced recovery after surgery comes from Angie Balfour and Ruth Alldridge, who discuss preoperative preparation, postoperative complications and the reality of being in hospital through to discharge and going home. Next, Thomas W. Wainwright, David A. McDonald and Louise C. Burgess describe the role of physiotherapy within ERAS and ICU. They note the need to increase the awareness and involvement of physiotherapists within the outpatient setting, as patients' physical weakness may persist after discharge. Frederic Michard describes recent innovations in cardiorespiratory monitoring, including smartphones and wearables, that can be used from prehabilitation and intraoperative use through to the rehabilitation period. A simple equation can be used to estimate how much hospitals could invest in such technology to improve quality of surgical care at no cost, he explains. Recent research into physical impairment in ICU patients is reviewed by Carrie M. Goodson, Claire Tipping and colleagues. They look at recent clinical trials evaluating physical rehabilitation during critical illness and interventions that may improve patient outcomes. Next, Paul E. Wischmeyer explains what the metabolism and caloric needs are for recovery after ICU, how nutrition delivery after ICU should be best delivered, and outlines the role of specific anabolic/anti-catabolic agents, vitamin D and the microbiome and probiotics in recovery. Just one week on mechanical ventilation can have a long-term deleterious effect on patients following discharge from the ICU. Matteo Parotto and Margaret S. Herridge review recent findings on outcomes, including the patient and family perspectives. Recovery after ICU can be assisted by innovative technology. Next, Sara Evans, Dhaneesha Navin Sannasgala Senaratne and Carl Waldmann discuss the gamut of technological innovations that promote survival and enhance recovery, covering weaning, communication, early mobilisation and the ICU environment through to continuity of care and specific issues after ICU. Finally, ten years on from her ICU stay due to sepsis, former nurse Idelette Nutma-Bade describes her path to recovery, which inspired her to write a book and run workshops to help other patients recovering from sepsis.

In our Matrix section, Megan M. Hosey, Janice J. Jaskulski and colleagues explain what animal-assisted activity and therapy are, how to incorporate these into a treatment plan, and outline the considerations for setting up such a programme. Christiaan Boerma considers issues with haemodynamic monitoring that are not often addressed in the literature, and explains how to improve implementation strategies for haemodynamic monitoring. Franceso Mojoli and Silvia Mongodi describe how to use point-of-care lung, diaphgragm and cardiac ultrasound to manage the mechanically ventilated patient, diagnose complications and integrate the information during the weaning phase. In our Management section, Todd Dorman urges us to leave the 'command and control' form of leadership in the past. He outlines modern approaches to leadership that will get the best from the ICU team in order to enhance patient and family care. Next, Tom J. Pollard and Leo Anthony Celi get beyond the hype to explain how to facilitate adoption of machine learning in critical care. Collaboration with other disciplines is vital, they say, as well as earning the trust of society to use and reuse data.

The *ICU Management & Practice* team will be at LIVES 2017 in Vienna. We hope to see you there!

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

Jean-Louis Vincent

Jean-Louis Vincent

Editor-in-Chief
ICU Management & Practice

Professor
Department of Intensive Care
Erasme Hospital / Free University of Brussels
Brussels, Belgium

JLVincent@icu-management.org

Reference

Vincent JL, Hall JB, Slutsky AS (2014) Ten big mistakes in intensive care medicine. Intensive Care Med, 41(3): 505-7.

COVER STORY

SPECIAL SUPPLEMENT (p. 159-170)

POINT OF VIEW

IN EVERY ISSUE

38th International Symposium on Intensive Care and Emergency Medicine

SQUARE - BRUSSELS MEETING CENTER
MARCH 20-23, 2018

Join us in 2018

Plenary Sessions, Mini-Symposia, Workshops, Technical Forums, Round Tables, Tutorials, Posters

CME ACCREDITED

Meeting Chairman: JL Vincent
Email: jlvincen@ulb.ac.be
Manager: V De Vlaeminck
Email:
veronique.de.vlaeminck@intensive.org
Dept of Intensive Care,
Erasme University Hospital
Route de Lennik, 808,
B-1070 Brussels, Belgium
Phone 32.2.555.32.15/36.31
Email: sympicu@intensive.com

Endorsed by:
European Society of Intensive Care Medicine
Society of Critical Care Medicine
American Thoracic Society
European Society for Emergency Medicine
European Shock Society
The Weil Institute of Critical Care Medicine
The Canadian Critical Care Society
Australian and New Zealand Intensive Care Society
International Pan Arab Critical Care Medicine Society
World Federation of Societies of Intensive and Critical Care Medicine
International Sepsis Forum

Hôpital Erasme | ULB | SIZ

http://www.intensive.org

MATRIX

MANAGEMENT

YOU ARE INVITED TO THE MEDTRONIC SIMULATION CENTER

PROGRAM

- How to recognise & intervene on patient-ventilation asynchonies
- Extracorporeal therapies in the ICU

SESSION TIME

Monday, 25th
14:15 - 15:15

Tuesday, 26th
11:45 - 12:45
16:45 - 17:45

Wednesday, 27th
11:45 - 12:45

REGISTRATION

Please register at Simulation Center with one of our Medtronic Representatives

LOCATION

The Simulation Center is located at Main Entrance of congress venue

Medtronic
Further, Together

The role of autophagy in recovery from critical illness

Jan Gunst
Assistant Professor

jan.gunst@kuleuven.be

Ilse Vanhorebeek
Associate Professor

ilse.vanhorebeek@kuleuven.be

Greet Van den Berghe
Full Professor

greet.vandenberghe@kuleuven.be

Clinical Division and Laboratory of Intensive Care Medicine
Department of Cellular and Molecular Medicine
KU Leuven
Leuven, Belgium

Increasing evidence implicates autophagy as repair process crucial for recovery from critical illness-induced vital organ failure and muscle weakness. This article summarises recent evidence and highlights potential implications for therapy.

Progress in intensive care medicine has resulted in improved survival from acute life-threatening conditions. Still, a considerable number of patients admitted to the intensive care unit (ICU) do not recover swiftly and remain dependent on support of failing vital organs for a prolonged period of time. These so-called prolonged critically ill patients face a high mortality risk and a considerable number of surviving patients suffer from important long-term debilities (Herridge et al. 2011). The underlying reasons why certain critically ill patients recover quickly, whereas others remain ICU-dependent, are incompletely understood. Despite the often severe organ failure and muscle weakness, overt cell death is rare in these patients (Hotchkiss et al. 1999). Furthermore, in patients surviving ICU stay, partial or full recovery of organ function is possible, even in organs with a poor regenerative capacity (Hotchkiss et al. 1999; Singer et al. 2004). Altogether, this observational evidence suggests that patients can recover from a life-threatening insult by activating cellular repair mechanisms. Increasing evidence implicates macroautophagy, hereafter referred to as autophagy, as a crucial repair process in critically ill states.

Autophagy is a catabolic process by which intracellular content is digested in the lysosome after delivery by an intermediate organelle, the autophagosome (Choi et al. 2013; Kroemer et al. 2010). Autophagy starts with the formation of isolation membranes in the cytoplasm, which elongate to surround cytoplasmic content, with formation of a vesicular structure, the autophagosome. Once mature, autophagosomes fuse with lysosomes, after which the engulfed content is degraded. Autophagy is induced by nutrient restriction, exercise and a variety of stress signals. Conversely, nutrients, insulin and other growth factors suppress it. Autophagy is crucial for maintaining homeostasis, by providing metabolic substrate in conditions of insufficient supply and/or increased demand (non-selective autophagy), and by clearing macromolecular structures that need to be removed or renewed (selective autophagy). Importantly, it is the only process able to clear damaged organelles, potentially toxic protein aggregates, and intracellular pathogens. The important housekeeping function of autophagy is illustrated by the severe organ dysfunction and tissue degeneration that develops when autophagy is tissue-specifically inactivated in adult mice, as demonstrated for numerous cell types, including hepatocytes, skeletal and cardiac myocytes, renal tubular cells and neurons (Levine et al. 2015).

Although autophagy was discovered more than 50 years ago, research interest in its therapeutic application mainly got attention in the last 15 years. This is explained by the increased knowledge in the molecular machinery involved and the evolved insights concerning the role of autophagy in physiology and pathology. Indeed, whereas autophagy was initially considered to be a cell death mechanism, apart from necrosis or apoptosis, most recent evidence clearly puts forward a protective role in normal physiology and in numerous disease states (Choi et al. 2013). Indeed, although some dying cells show substantial increases in autophagosomes, cells may be dying despite, rather than because of, active autophagy. Moreover, since autophagy activation attenuates rather than accelerates cell death, autophagy activation is now considered to be adaptive in conditions of cellular stress (Hotchkiss et al. 2009).

Evidence supporting a role of autophagy in critical illness

A variety of cellular stressors, which are frequently encountered during critical illness, stimulate autophagy. These include hypoxia and ischaemia, inflammation, endoplasmic reticulum stress, oxidative stress and mitochondrial damage (Kroemer et al. 2010). In line with the historical concept of autophagic cell death, early observational studies attributed the sepsis-induced organ damage to the

concomitant appearance of autophagosomes (Watanabe et al. 2009; Watts et al. 2004). However, causality remained unproven, since these early studies did not interfere with the process. Alternatively, cell damage may have been present despite activation of autophagy, or autophagy activation may have been insufficient to cope with the damage. Moreover, theoretically, autophagosomes may also accumulate when fusion with the lysosome is hampered.

Recently, as for many other diseases, a considerable number of studies have shown a protective role of autophagy against critical illness-induced organ failure. A pioneer study on liver and muscle biopsies harvested from prolonged critically ill patients clearly demonstrated hallmarks of insufficient autophagy activation (Vanhorebeek et al. 2011). Indeed, in both tissues, autophagic substrates accumulated in combination with a reduced formation of autophagosomes, as evidenced ultrastructurally and by a molecular marker of autophagosome formation. Concomitantly, both liver and muscle displayed severe (ultra)structural damage, with accumulation of damaged mitochondria and aberrant membranous structures in liver, and vacuolisation of muscle fibres. All these changes mimic the phenotypical changes that were observed in mice with a liver- or muscle-specific knockout of key autophagy genes (Komatsu et al. 2005; Masiero et al. 2009).

A subsequent study confirmed the autophagy-deficient phenotype in skeletal muscle of prolonged critically ill patients and found that the degree of insufficient autophagy significantly correlated with the incidence of ICU-acquired muscle weakness (Hermans et al. 2013). Although observational, these data support the functional relevance of autophagy activation in critically ill patients. In line with this, a recent study found an increased autophagic response in leucocytes from patients surviving septic shock, as compared to non-survivors, which corresponded with an improved neutrophil function in survivors (Park et al. 2017).

Animal data have confirmed the functional importance of autophagy activation in response to severe physical stress by interfering with the process. As in patients, a similar autophagy deficiency phenotype was observed in liver and kidney of critically ill rabbits, and the degree of insufficient autophagy correlated with the risk of mortality and the degree of organ dysfunction (Gunst et al. 2013). Thereafter, in an intervention study, administration of the autophagy activator rapamycin stimulated autophagy and protected against vital organ dysfunction and bone loss (Gunst et al. 2013; Owen et al. 2015).

Subsequently, numerous rodent studies have confirmed a protective role of autophagy against organ failure in different models of critical illness. Indeed, these animal studies showed that active autophagy attenuated sepsis-induced mortality and sepsis- or endotoxin-induced cardiac, pulmonary, renal, hepatic and neuronal damage (Hsieh et al. 2011; Lalazar et al. 2016; Li et al. 2017; Lo et al. 2013; Mei et al. 2016). Moreover, active autophagy was found to be crucial for an intact immune function, whereas insufficient autophagy resulted in lymphocyte apoptosis (Lin et al. 2014; Oami et al. 2017; Park et al. 2017; Pu et al. 2017).

> **Studies have shown a protective role of autophagy against critical illness-induced organ failure**

In addition, activated autophagy protected against ischaemia-reperfusion injury in heart, liver, kidney and brain, and was identified as a protective mechanism involved in ischaemic preconditioning (Gao et al. 2015; Li et al. 2016; Liu et al. 2012; Papadakis et al. 2013; Wang et al. 2011). Active autophagy also attenuated toxic liver and kidney injury (Ding et al. 2010; Takahashi et al. 2012). Hence, animal models support an essential role of autophagy in allowing recovery from a severe insult and thus, autophagy emerges as a potentially important therapeutic target in critical illness.

Autophagy as therapeutic target

Several strategies could theoretically be applied to improve autophagy activation during critical illness, such as its pharmacological activation or modulation by metabolic interventions.

Pharmacological activation of autophagy

In animal models, the causal involvement of activated autophagy in alleviating critical illness-induced organ failure was demonstrated by genetic manipulation (selectively knocking out or overexpressing key autophagic genes) and by pharmacological interference (by administering autophagy activators and/or inhibitors) (Ding et al. 2010; Gao et al. 2015; Gunst et al. 2013; Hsieh et al. 2011; Lalazar et al. 2016; Li et al. 2016; Li et al. 2017; Lin et al. 2014; Liu et al. 2012; Lo et al. 2013; Mei et al. 2016; Oami et al. 2017; Papadakis et al. 2013; Park et al. 2017; Pu et al. 2017; Takahashi et al. 2012; Wang et al. 2011). Currently, however, no autophagy activators are readily available for study in critically ill patients. Indeed, although several registered drugs have been identified as potential autophagy activators, all lack specificity (Levine et al. 2015) and several of these drugs have other, non-negligible pharmacological effects that preclude unselected use in critically ill patients. For instance, rapamycin, the most widely used autophagy activator, has potent immune-suppressive effects. In addition, for other drugs, the autophagy-stimulating potential has not been confirmed in critically ill animal models. Future research should aim at identifying novel, more specific autophagy activators that are suitable for study in ICU patients.

Modulation of autophagy by metabolic interventions

Apart from direct pharmacological activation, autophagy can also be affected via metabolic interventions during critical illness. Indeed, nutrition and treatment of hyperglycaemia with insulin therapy have been shown to modulate autophagy in critically ill patients and animal models (Derde et al. 2012; Gunst et al. 2013; Hermans et al. 2013; Vanhorebeek et al. 2011).

In normal physiology, nutrition is a strong suppressor of autophagy. A randomised controlled trial has shown that, also in critically ill patients, autophagy was suppressed in muscle by giving early parenteral nutrition (PN), with the degree of autophagy suppression correlating with an increased incidence of muscle weakness (Hermans et al. 2013). In this study, early PN also hampered recovery from muscle weakness, as compared to withholding PN until one week after ICU admission. A randomised animal study demonstrated that especially the amino acid content of early PN suppressed autophagy, more than glucose or

lipids (Derde et al. 2012). This may explain why both adult and paediatric studies statistically attributed the harm of early PN observed in two large randomised controlled trials to the administration of amino acids, and not to the other macronutrients (Casaer et al. 2013; Vanhorebeek et al. 2017).

On the one hand, insulin is another well-known suppressor of autophagy, apart from nutrition. On the other hand, hyperglycaemia may induce glucose overload in organs with insulin-independent glucose uptake, such as the brain, liver, kidney and immune cells, which may also suppress autophagy. Hence, lowering blood glucose concentrations with insulin therapy during critical illness may impact on autophagy in two directions. Currently, the net impact on autophagy remains unclear, since mechanistic studies have revealed conflicting results. A patient study found a neutral or possibly negative impact on autophagy by tight blood glucose control (Vanhorebeek et al. 2011). Indeed, in postmortem liver and postmortem and in vivo muscle biopsies sampled from prolonged critically ill patients randomised to tight (targeting 80-110 mg/dl) or liberal (tolerating hyperglycaemia up to 215 mg/dl) blood glucose control, molecular hallmarks of insufficient autophagy were equally present in both randomisation groups. Ultrastructurally, however, there was a greater reduction in the number of autophagic vacuoles in the liver of deceased critically ill patients randomised to tight blood glucose control, as compared to liberal blood glucose control. In contrast, an animal study clearly showed improved autophagy by prevention of hyperglycaemia with insulin therapy (Gunst et al. 2013). Apart from a species difference, a major difference between the animal and the human study is the degree of hyperglycaemia, which was more severe in the animal study. Importantly, both human and animal studies included the use of early PN and in this context, prevention of hyperglycaemia with insulin resulted in a protection against cellular damage, as shown by prevention of ultrastructural damage to mitochondria, an improved mitochondrial function and an improved organ function (Vanhorebeek et al. 2005; Vanhorebeek et al. 2009). Hence, in a context of early PN, the balance between genesis and removal of cellular damage was in favour of tight blood glucose control with insulin therapy, even if the net impact of the intervention on autophagy remains unclear. The impact of the intervention on autophagy and cell damage in the absence of early PN remains unclear.

Conclusion

Increasing evidence implicates autophagy as a crucial cellular repair process necessary to survive critical illness. Hence, autophagy emerges as a potentially important therapeutic target. Currently, no specific autophagy activators are available, which are needed before human studies can be initiated. Withholding PN in the early phase of critical illness shortens ICU dependency, which may be mediated via its stimulating impact on autophagy. ■

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

Ilse Vanhorebeek and Greet Van den Berghe have received research grants from the Research Foundation Flanders (Belgium, G.0592.12N) and the Methusalem Programme (funded by the Flemish Government, METH/14/06). Greet Van den Berghe has received a research grant from the European Research Council (ERC) under the European Union's Seventh Framework Programme (FP7/2013–2018 ERC Advanced Grant Agreement number 321670). Jan Gunst receives a postdoctoral research fellowship supported by the Clinical Research Fund of the University Hospitals Leuven.

Abbreviations

ICU intensive care unit
PN parenteral nutrition

References

Casaer MP, Wilmer A, Hermans G et al. (2013) Role of disease and macronutrient dose in the randomised controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med, 187(3): 247-55.

Choi AM, Ryter SW, Levine B (2013) Autophagy in human health and disease. N Engl J Med, 368(19): 1845-6.

Derde S, Vanhorebeek I, Güiza F et al. (2012) Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology, 153(5): 2267-76.

Ding WX, Li M, Chen X et al. (2010) Autophagy reduces acute ethanol-induced hepatotoxicity and steatosis in mice. Gastroenterology, 139(5): 1740-52.

Gao C, Cai Y, Zhang X et al. (2015) Ischaemic preconditioning mediates neuroprotection against ischaemia in mouse hippocampal CA1 neurons by inducing autophagy. PLoS One, 10(9): e0137146.

Gunst J, Derese I, Aertgeerts A et al. (2013) Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. Crit Care Med, 41(1): 182-94.

Hermans G, Casaer MP, Clerckx B et al. (2013) Effect of tolerating macronutrient deficit on the development of intensive care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med, 1(8): 621-9.

Herridge MS, Tansey CM, Matté A et al. (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med, 364(14): 1293-304.

Hotchkiss RS, Strasser A, McDunn JE et al. (2009) Cell death. N Engl J Med, 361(16): 1570-83.

Hotchkiss RS, Swanson PE, Freeman BD et al. (1999) Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med, 27(7): 1230-51.

Hsieh CH, Pai PY, Hsueh HW et al. (2011) Complete induction of autophagy is essential for cardioprotection in sepsis. Ann Surg, 253(6): 1190-200.

Komatsu M, Waguri S, Ueno T et al. (2005) Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. J Cell Biol, 169(3): 425-34.

Kroemer G, Mariño G, Levine B (2010) Autophagy and the integrated stress response. Mol Cell, 40(2): 280-93.

Lalazar G, Ilyas G, Malik SA et al. (2016) Autophagy confers resistance to lipopolysaccharide-induced mouse hepatocyte injury. Am J Physiol Gastrointest Liver Physiol, 311(3): G377-86.

Levine B, Packer M, Codogno P (2015) Development of autophagy inducers in clinical medicine. J Clin Invest, 125(1): 14-24.

Li S, Liu C, Gu L et al. (2016) Autophagy protects cardiomyocytes from the myocardial ischaemia-reperfusion injury through the clearance of CLP36. Open Biol, 6(8): pii: 160177.

Li Y, Wang F, Luo Y (2017) Ginsenoside Rg1 protects against sepsis-associated encephalopathy through beclin 1-independent autophagy in mice. J Surg Res, 207: 181-9.

Lin CW, Lo S, Hsu C et al. (2014) T-cell autophagy deficiency increases mortality and suppresses immune responses after sepsis. PLoS One, 9(7): e102066.

Liu S, Hartleben B, Kretz O et al. (2012) Autophagy plays a critical role in kidney tubule maintenance, aging and ischaemia reperfusion injury. Autophagy, 8(5): 826-37.

Lo S, Yuan SS, Hsu C et al. (2013) Lc3 over-expression improves survival and attenuates lung injury through increasing autophagosomal clearance in septic mice. Ann Surg, 257(2): 352-63.

Masiero E, Agatea L, Mammucari C et al. (2009) Autophagy is required to maintain muscle mass. Cell Metab, 10(6): 507-15.

Mei S, Livingston M, Hao J et al. (2016) Autophagy is activated to protect against endotoxic acute kidney injury. Sci Rep, 6: 22171.

Oami T, Watanabe E, Hatano M et al. (2017) Suppression of T cell autophagy results in decreased viability and function of T cells through accelerated apoptosis in a murine sepsis model. Crit Care Med, 45(1): e77-85.

Owen HC, Vanhees I, Gunst J et al. (2015) Critical illness-induced bone loss is related to deficient autophagy and histone hypomethylation. Intensive Care Med Exp, 3(1): 52.

Papadakis M, Hadley G, Xilouri M et al. (2013) Tsc1 (hamartin) confers neuroprotection against ischaemia by inducing autophagy. Nat Med, 19(3): 351-7.

Park SY, Shrestha S, Youn YJ et al. (2017) Autophagy primes neutrophils for neutrophil extracellular trap formation during sepsis. Am J Respir Crit Care Med, 30 March. doi: 10.1164/rccm.201603-0596OC. [Epub ahead of print]

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

Intensify nutrition in the ICU to help him

enjoy life again

PEPTAMEN® INTENSE provides the full performance of PEPTAMEN®, tailored to the metabolic needs of your ICU patients.

PEPTAMEN® INTENSE is shown:
- To achieve protein goals without overfeeding ICU patients [1,2]
- To facilitate blood glucose management in ICU patients [3,4]

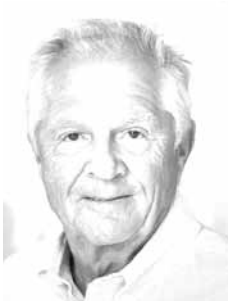
1. Hopkins B & Jackson N. JPEN. 2017; S46: p54. ASPEN CNW Abstract. **2.** Wieser, Cohen, Ochoa J, Huhmann M. JPEN. 2017. ASPEN CNW Abstract. **3.** McClave S, et al. ASPEN CNW 2015 (Abstract) **4.** Ochoa, et al. ASPEN CNW 2017 (Poster/Abstract)

INTRODUCING

Nestlé Health Science

PEPTAMEN® INTENSE

High performance.
Improved outcomes.



Henrik Kehlet
Professor
Head of Section for
Surgical Pathophysiology
Rigshospitalet
Copenhagen, Denmark

Henrik.Kehlet@regionh.dk

Fast-Track Surgery

A Multidisciplinary Collaboration

Prof. Henrik Kehlet reflects on the progress of fast-track surgery and the need for multidisciplinary teamwork in optimising perioperative care.

You are the "father" of fast-track surgery. What motivated you to develop this concept?

It all started when I was a young surgeon and had to perform some major operations. The technical aspects of surgery went well, but patients developed medical complications like myocardial infarction or pulmonary embolism. I started to question why, if you do it well, there should be a risk for these medical complications. Then it all started step by step—pain management, fluid management, nursing care etc. etc. It was a stepwise development, based on the simple question of why patients have a risk of a medical complication if the surgery was successful technically.

How do you see the progress of fast-track surgery?

This was developed in major colonic surgery more than 20 years ago, and published in the *Lancet* (Bardram et al. 1995). In the beginning it had a very slow uptake, because people didn't believe it. In the last five years there has been major attention to this concept, and there are societies on fast track or enhanced recovery in many parts of the world. It is catching on, but as usual in medicine and healthcare it takes time, because the cultural and economic aspects are different between countries and the different professions. That's the main explanation for delayed acceptance and implementation. But now everybody agrees that this is right and it moves forward.

What is the business case for fast-track surgery? How should any cost savings be shared?

This is a very important and complicated question. Everybody agrees that you save money, because hospital stay is decreased and the risk of medical complications decreases. There are also benefits post-discharge, because patients are in better condition and rehabilitation is facilitated. Then it begins to be complicated, because if you decrease length of stay who will get the money? This is different in different countries, but all agree that you save money. In the beginning I experienced that when we reduced hospital stay the hospital administration either sent in medical patients with brain injury to surgical departments, which killed our department because of the workload, or they closed the beds without thinking that those patients who remain in the department are always a little more sick than the general population before. Thus, administration allocates so much money per bed and so many nurses per bed and that can create a problem. In the end we agreed that savings should be shared so that further development can be instituted, for instance by giving support for a research nurse or a PhD student etc. This requires collaboration between the administration, the hospital and the surgical departments, but this is difficult. In some countries, for example Germany, the reimbursement system is such that if you do surgery too well, too fast, you are punished, and get less money. That prevents development. There is no simple answer because countries have different economic and reimbursement systems. What is happening now, especially in the U.S., is the concept of bundled care payment. That means that the hospital gets a given amount of dollars to cover everything that happens within the first 30 days. Therefore they have to optimise, because before they got money for the hospital stay, and if the patient was readmitted after 14 days they got more money. The new system will be that you have to optimise care, because you get given a certain amount of dollars whatever happens. Whatsoever, the basic conclusion is definite, you save money with the concept. It's a very unique combination that you increase quality of care and at the same time save money; this is not common in healthcare.

Who should start the process of implementing enhanced recovery after surgery programmes?

I am getting older and have been disappointed with the speed of implementation. Ideally it should start locally with the heads of surgery, anaesthesia and nursing. These are the people who take care of patients. If it doesn't work, of course the hospital leadership should monitor what is going on in their own hospital, compared to other places in the world. If there is a huge discrepancy then the hospital leaders must go in and stimulate the departments of surgery, anaesthesia and nursing. If the hospitals don't do it, then the last step is the government. Again history has shown a huge variability; sometimes it starts fantastically in the

departments, sometimes very slow, sometimes hospital leaders go in, sometimes not. Here in Denmark we had support from the government in the beginning to improve knowledge and implementation of nursing care. In England they also received funding to monitor the data and outcomes in a certain number of operations and that facilitated the process.

Is there a potential for 'turf wars'?

In perioperative medicine, including fast-track surgery, there is a power play as to which profession should lead all this. In some countries they have started organisations totally focused on anaesthesiologists, and this was why I wrote an editorial in the *British Journal of Anaesthesia* against that (Kehlet et al. 2015), because from the very beginning the concept is based upon multidisciplinary collaboration. Therefore we should not say from the beginning it has to be surgeons who should lead this, or anaesthesiologists or nurses. It is a joint effort. Therefore in some hospitals the key person who has the knowledge should lead it and it may be another profession in another place. We shouldn't have this power play that it's all based on a given profession as that is not fruitful or positive to increase implementation of knowledge. The previous editorial from anaesthesiologists (Cannesson et al. 2015) was very provocative; they didn't even mention the word surgeon, despite the fact that it was a surgeon who developed the concept. This is not about a power game between the professions. It's about facilitating the concept. Locally it can be anyone who has knowledge and the ability to work together.

How can enhanced recovery programmes affect admissions to intensive care following surgery?

Ideally the purpose of the concept is to avoid postoperative organ dysfunction. Consequently the need for postoperative intensive care should decrease. The data have shown worldwide that the risk of medical complications decreases, but they are not eliminated. Consequently, there are implications for the need for intensive care beds. The unsolved question is about the need for semi-intensive or intermediate care beds. The studies on enhanced recovery mostly come from elective surgery. Unfortunately, there are only a few studies on hip fracture and acute abdominal surgery so we have a black spot of knowledge about fast-track emergency surgical procedures and the need for intensive care beds.

You have made recommendations on reporting of enhanced recovery elements in clinical studies. Please comment.

The ERAS® society has published many guidelines on enhanced recovery and they always include a large number of elements of care. This is a problem, because if you go to a department and say you have to modify or change 23 elements of care, it is very difficult. I see this in all the places I visit that one problem with implementation is the too many elements. Not all are sufficiently evidence-based, so future efforts should go to implement enhanced recovery after surgery (ERAS) as simply, pragmatically and as evidence-based as possible. Other smaller elements can be researched by interested people to find out if they are important in this or that operation. For example, if people believe that preoperative glucose load is crucial, they have to do the research. If you look at the literature every month reports come out that compliance with the ERAS recommendations is 70 percent or so. This doesn't help us. We have to focus on the few elements that are really important, as we showed more than 20 years ago.

> "I am getting older and have been disappointed with the speed of implementation"

For enhanced recovery, the number of elements really necessary depends on the type of surgery. In joint replacement surgery it's almost all about pain management, organisation and information, because you don't have the pronounced physiological disturbances with impaired pulmonary function, ileus etc.

Part of the concept of enhanced recovery is providing information to patients and families. How is this done?

When we started in Denmark, we had some television programmes with the patients and me. There may be potential negative reactions to shortening length of stay. People may think they are discharged from hospital too early, which is not the case. We treat them better, they are better and therefore they can go home faster. The key element is to inform the patients and relatives ahead of time—not the day they come in for surgery, but when the indication for surgery is made. Then they should have information about the care programme, how they should be involved, what the expected length of stay is and the discharge criteria. This information is crucial, otherwise it will not work. They have to participate in the programme, they have to understand what is going on. You can also have patient education videos or patient classes. If you have a high-volume orthopaedic department with many hip and knee replacements, you can get patients together or even include a patient who was operated on a week before, to let them see. Again it has to be individualised, depending on the disease and the procedure. ■

References

Bardram L, Funch-Jensen P, Jensen P et al. (1995) Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet, 345(8952): 763-4.

Cannesson M, Ani F, Mythen MM et al. (2015) Anaesthesiology and perioperative medicine around the world: different names, same goals. Br J Anaesth, 114(1): 8-9.

Kehlet H, Delaney CP, Hill AG (2015) Perioperative medicine – the second round will need a change of tactics. Br J Anaesth, 115(1): 13-4.

Angie Balfour
Enhanced Recovery Research Nurse
Colorectal Unit
Western General Hospital
NHS Lothian
Edinburgh, Scotland

angie.balfour@nhslothian.scot.nhs.uk

@Balfoor

Ruth Alldridge
Senior Physiotherapist
Colorectal Unit
Western General Hospital
NHS Lothian
Edinburgh, Scotland

ruth.alldridge@nhslothian.scot.nhs.uk

The patient voice in Enhanced Recovery After Surgery

An Edinburgh perspective

This article will explore the ERAS Programme and provide a unique insight into perspectives and realities of surgical recovery. It will highlight the current evidence versus patients' perceptions and expectations.

Background

The Enhanced Recovery After Surgery (ERAS) programme has been implemented in many surgical units around the world over the last two decades with varying degrees of success. This evidence-based multimodal programme is known to reduce length of hospital stay and reduce postoperative complications following elective surgery. This is clearly an attractive concept both for healthcare providers and for individual patients; however, despite the extensive evidence base, clinical variation still exists in surgical departments. Over the last several years, surgeons are performing more minimal access surgery, anaesthetists are prescribing and administering multimodal, opioid-sparing regimes, but has sufficient attention been given to patient preparation? And have the changes in surgical management been disseminated to the people that healthcare serves—the patients?

ERAS has its origins in colorectal surgery, and it is widely accepted that reduction of surgical stress, maintenance of physiological function and accomplishing early mobilisation are cornerstones of ERAS. Better compliance with these principles results in improved recovery and is reflected in shorter length of hospital stay and a reduction in complications (Gustafsson et al. 2013). In Edinburgh, Professor Ken Fearon was a key driver of ERAS and was one of the founding members of the ERAS® Society. The Western General Hospital in Edinburgh remains heavily involved in ongoing work to promote and progress ERAS principles both nationally and internationally.

A key aspect of the ERAS programme is the preoperative preparation and involvement of patients and their families. This should ideally lead to patients being more empowered and their expectations of surgical recovery being more realistic. However, this process can be challenging and requires a robust patient-centred approach to ensure that the *right* information is given to patients at the *right* time using the *right* format. In order to represent the patient voice and to highlight the realities of surgical recovery, a video interview was conducted between an ERAS nurse and a colorectal patient – Ruth.

Several topics were selected for discussion with Ruth during an informal, semi-structured interview to explore her experiences leading up to surgery and the recovery thereafter. Ruth is also a physiotherapist who works in the colorectal unit where she was unfortunately diagnosed with bowel cancer and required surgery. This gives her a unique perspective on both the importance of the ERAS programme from a healthcare professional point of view and from the patient perspective.

Interview

The interview was conducted using questions that were formulated from the experiences of several members of the local clinical team who had also had surgery recently. The key themes of these discussions were around preoperative preparation, being a patient, the discharge process and going home, and specific postoperative complications such as ileus. Other issues such as sleep deprivation and environmental realities of being in hospital were also raised.

The interview was an informal chat around these issues that was captured on video and then presented at the ERAS Congress in Lyon in May 2017. The patient voice is a crucial component of the ERAS programme that we were keen to highlight, because in some circumstances, despite the best intentions of the multidisciplinary team (MDT), delivery of the ERAS care pathway is challenging, particularly when issues such as pain or gut dysfunction hinder the patient's ability to adhere to all the aspects of ERAS. The key areas of the discussions are described under the following headings:

Preoperative preparation

It is often assumed that providing preoperative information is either simple or already embedded in standard practice. From the patient's perspective, being well prepared for surgery sets the expectations of how recovery should progress and will ultimately enhance the overall journey through the surgery, hospital stay and beyond. During the interview with Ruth, it was clear that certain parts of the preoperative information were appropriately delivered and well received by

Mastering the art of Anaesthesiology

Introducing a fresh new orchestra of trusted anaesthesia products by **Aspen**.
Unifying an ensemble of 20 exceptional brands and over 150 original product formulations,
Aspen supports you in the orchestration of a safe and positive
clinical experience for your patients and your organisation.

EUCIS-DIPR-0417-0169

Product and formulation may not be available in all countries. For full safety, please refer to the nationally approved summary of product characteristics and ask your local Aspen representative for more information.

aspen

Successful **patient experience** begins here

her and her family and that they framed the forthcoming process succinctly. This information was delivered by the surgeon, who took into account that Ruth was a healthcare professional, but that he was going to give her, the same information as he would give any other patient. This was person-centred for her, and providing generic information was much appreciated and entirely appropriate in this case.

The information given following the initial consultation was felt to be heavily paper-based; Ruth admitted that she didn't read the majority of the booklets. We discussed this, and concluded that there may be better ways of delivering preoperative information. An app, access to video information or perhaps a face-to-face education class would be more appropriate for certain patients. We touched on whether being a healthcare professional altered the information she was given as there may have been pre-conceived ideas that she knew what was about to happen and so did not require the same level of information. This was not experienced until after her operation, where she almost felt 'reined in', as staff in the high dependency unit were obviously aware that she was a physiotherapist and were concerned that she may 'overdo' the mobilisation part of her recovery.

Hospital admission

In this case, there were obviously expectations of the ERAS process and Ruth had set herself goals around her recovery. There were understandable anxieties around changing roles from healthcare professional to patient—being treated by people she saw as peers and colleagues and potentially sharing ward space with ex-patients. This was alleviated somewhat by providing a single room in the ward area. During her hospital stay, there were key themes that were highlighted that she felt were difficult aspects of her recovery.

Sleep deprivation

Sleep is challenging in a hospital environment and is perhaps mismanaged in some instances. Ruth was able to highlight how she didn't fully appreciate how profound an effect this would have on her recovery. She commented that in hindsight it would have been better to have this highlighted earlier in her preoperative preparation and mentioned that although her pain was managed very well, she used analgesia knowing that it would result in a period of sleep and alleviate her nausea. We discussed the need to highlight this as an issue and perhaps recommend that patients are supplied with simple strategies such as eye masks and earplugs and that they discuss any sleep issues with staff.

"requires a robust patient-centred approach to ensure that the *right* information is given to patients at the *right* time using the *right* format"

Mobility and Restricted Independence

Because Ruth is a physiotherapist, she was all too aware of the importance of mobilisation and ERAS targets. However, she described how she would have preferred to walk as opposed to sitting in a chair for a set period of time. It is perhaps the case that walking is not offered to patients for a variety of reasons, and sometimes the desire for staff may be to follow the ERAS pathway, which contains certain compliance measures such as being up to sit for 4 hours on post-op day one. Ruth felt that some of the ERAS processes are a bit too prescriptive and suggested that a more person-centred approach should be offered. Being aware of each patient's capabilities is crucial and the sheer exhaustion following surgery means that it may not be appropriate to meet the targets with that particular patient on that particular day. Ruth described this sensation of fatigue as "*walking in glue*".

Ruth also commented:

"…..I think any element of normality that was added in during my stay in hospital always felt good. I think any patient would probably feel that way……putting on your own clothes, being able to get up and walk to the toilet on your own. All these things are hugely important to how you feel and then you're not the vulnerable person, getting stuff done to you—you regain your independence"

This sentiment that Ruth wished to regain normality is very powerful and really important. However, it is not always possible due to other circumstances such as intravenous fluids left up and catheters not being removed when appropriate.

Diet and associated challenges

This issue was by far the most challenging aspect of Ruth's recovery (including her chemotherapy treatment) as she developed a postoperative ileus.

She recognised the need to eat and drink soon after surgery in order to minimise gut dysfunction so she ate soon after surgery, but within 48 hours she began to vomit, and despite her best intentions, she was no longer able to eat or drink, so had a nasogastric tube inserted and IV fluids recommenced which was the main reason for her immobility. She described her experience as:

"…the time that I felt physically the worst, mentally the worst—it was terrible!! Unrelenting nausea, sickness, being limited in what I could do because of various attachments that came along with having an ileus. Knowing what I should be doing and not being able to do it. Knowing that I should be eating and being constrained. I can't even describe how awful it feels … it's just unrelenting is really the only way I can describe it."

She describes how she felt throughout this time and the relief when it finally came to an end:

"…I think it's just all-encompassing. Usually with pain, there's something you can take or there's a position you can get yourself into to relieve it. There's no relief from that feeling of nausea and then when it stopped, it was like a switch was flipped and I just felt better. I opened my eyes and I felt better. It was an incredible feeling and I think passing this on to anybody else, that they know it will end. I've seen people with postop ileus in a professional capacity so I knew even though in the moments of it, I just thought when, when is it going to finish?"

During this time when Ruth was unable to eat, she became increasingly fatigued and lost a significant amount of weight, which for a fit and healthy girl was a rather shocking sight for her family and friends (and her!!) to witness. The message emphasised here is that gut dysfunction is a significant barrier to recovery, and ultimately for Ruth led to a longer stay in hospital and delayed her overall recovery. We discussed whether this potential complication should be emphasised more at the preoperative stage, but Ruth felt that no-one could have described or made her understand just how unwell she would feel, and knowing more would not have helped her cope with this complication.

Going Home

The interview concluded by asking Ruth how she felt when she was given the green light to go home. Unsurprisingly, she felt that going home was when her real recovery began. She acknowledged that being able to eat what she wanted, sleep normally and go out for a walk, which may seem like simple tasks, all added to regaining a sense of normality.

Conclusion and recommendations

Although the purpose of this video was for presentation at the ERAS 2017 congress, it has been an excellent resource to increase staff awareness about the realities surrounding hospital admission, the patient experience and the often unrealistic expectations of clinical staff, patients and the wider population.

The ERAS programme is widely recognised as evidence-based healthcare; however, it must be targeted appropriately and the individual needs and capabilities of each patient should be considered as opposed to a protocolised 'tick-box' process.

Recommendations highlighted during this process include considering alternative methods such as preoperative classes to deliver patient information, methods to reduce sleep-related difficulties and consideration around individualising patient care within an ERAS programme. ■

References and Further Reading

Fearon KC, Ljungqvist O, Von Meyenfeldt M et al. (2005). Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection." Clin Nutr, 24(3): 466-77.

Gustaffson UO, Scott MJ, Schwenk W et al. (2013). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg, 37 (2): 259–84.

Jones EL, Wainwright TW, Foster JD et al. (2014) A systematic review of patient reported outcomes and patient experience in enhanced recovery after orthopaedic surgery. Ann R Coll Surg Engl, 96(2): 89-94.

Taylor C, Burch J (2011) Feedback on an enhanced recovery programme for colorectal surgery. Brit J Nurs, 20(5): 286-90.

Vandrevala T, Senior V, Spring L et al. (2016). 'Am I really ready to go home?': a qualitative study of patients' experience of early discharge following an enhanced recovery programme for liver resection surgery." Support Care Cancer 24(8): 3447-54.

Thomas W. Wainwright
Associate Professor
in Orthopaedics
Bournemouth University
Bournemouth, UK

twainwright@bournemouth.ac.uk

@twwainwright

David A. McDonald
Service Improvement Manager
Scottish Government
Edinburgh, UK

david.mcdonald@nhs.net

Louise C. Burgess
Research Assistant
Bournemouth University
Bournemouth, UK

lburgess@bournemouth.ac.uk

The role of physiotherapy in Enhanced Recovery After Surgery in the intensive care unit

Enhanced recovery after surgery (ERAS) is an evidence-based, multimodal approach to optimising patient outcomes following surgery. The role of physiotherapy within ERAS and intensive care units (ICU) is important. Patients admitted to an ICU following elective major surgery may suffer from physical, psychological and cognitive problems, which can impact their return to function and quality of life. ICU physiotherapists can enable patients to achieve ERAS programme aims throughout their stay in an ICU and this may accelerate the achievement of discharge criteria and subsequent return to function. Functional limitations and persistent weakness may exist long after discharge, and therefore there is a need to increase the awareness and involvement of physiotherapists within the outpatient setting. Establishing a standardised rehabilitation programme, informed by key ERAS principles and delivered by specialist physiotherapists supported by a well-informed ICU team can have long-term benefits to patients post-discharge.

Enhanced recovery after surgery (ERAS) is a combination of perioperative care components built upon a multimodal approach that integrates evidence-based interventions to reduce convalescences across multiple surgical procedures. Since ERAS was first implemented within hospitals over twenty years ago, post-surgical outcomes have improved for patients (Kehlet and Wilmore 2008). Length of stay has decreased, with no subsequent increase in readmission rates (Paton et al. 2014), with concurrent improvements in clinical outcomes whilst having a beneficial impact on healthcare resources. ERAS programmes are supported by evidence-based preoperative, intraoperative and postoperative procedures to accelerate the achievement of discharge criteria. ERAS originated in elective colorectal surgery, but has spread to other surgical subspecialties, including, but not limited to, gastrointestinal, hepatobiliary, orthopaedic, cardiac, thoracic, head and neck, breast and gynaecologic surgery.

Physiotherapy and ERAS

The role of physiotherapy within ERAS pathways is important in both preoperative and postoperative routines. Implementing a preoperative strength programme has been shown to promote musculoskeletal improvements in preparation for a forthcoming physiological stressor (Carli et al. 2010), and is an emerging key component of ERAS. A literature review found preoperative exercise in patients scheduled for cardiovascular, thoracic, abdominal and major joint replacement surgery to be well tolerated and effective (Hoogeboom et al. 2014). Postoperative exercise programmes are also recommended by ERAS guidelines, promoting muscle hypertrophy and the return to function after major surgery (ERAS Society 2017).

Early postoperative mobilisation is a fundamental principle of good physiotherapy practice and of ERAS programmes. It has been shown to reduce the rate of morbidity and length of stay following major surgery (Epstein 2014; Kehlet and Wilmore 2008), with immobilisation due to hospitalisation causing a decline in muscle strength, insulin adherence and functional ability. Early mobilisation can accelerate the achievement of discharge criteria, and has been evidenced to reduce the rate of postoperative pulmonary complications, venous thromboembolism and infection (Epstein 2014). Early mobilisation can only be achieved through adequate pain control; multimodal opiod-sparing regimes, which are central to ERAS programmes are essential. This is a fundamental principle with-

FLUIDS ARE PERFECTLY SAFE
AND EASY TO MANAGE, RIGHT?

NOT SO FAST!

50 % of your patients do **not** respond to fluid,
how do you detect them **before** giving fluids?[1]

FLUIDS SHOULD BE TITRATED TO PATIENT RESPONSE.
LIKE ALL OTHER DRUGS.

Fluid management is vital to patient care.
Over – or under – resuscitation may result in tissue edema, increased risk of mechanical ventilation, more ICU days, organ failure, and possibly death[2].

You can't afford to wait!
Start monitoring your patient's status centrally and noninvasively with Cheetah Starling SV™.

VISIT OUR BOOTH AT ESICM VIENNA
25TH - 27TH SEPTEMBER

[1] *Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: A systemic review and meta-analysis. Intensive Care Medicine 2016; 1-13.*
[2] *Dr. Audrey Horne, "Fluids and Patient Outcomes", International Medicine Journal 25, no. 2 (August 2014): 320-50.*

cheetah medical™
cheetah-medical.com

in ERAS, in that each intervention, whether surgery and/or analgesic regimens, must consider its impact on rehabilitation goals and how to best support early postoperative mobilisation. There are many surgery-specific barriers to early mobilisation, highlighting the importance of a multidisciplinary care team approach.

Intensive care unit stay

A patient may be admitted to an intensive care unit (ICU) after elective major surgery if they require postoperative support either due to the complexity of surgery, or because of co-existing medical conditions. ICU admission is not always routine amongst all major surgeries that adopt ERAS principles, with orthopaedic procedures generally being the most well-tolerated by patients, and consequently rarely requiring ICU admission (AbdelSalam et al. 2012). ERAS guidelines highlight that gynaecologic, cardiac, pancreaticduodenectomy, colorectal, hepatic and head and neck cancer patients may require transfer to an ICU, depending upon their condition following surgery. Admission to an ICU is patient- and surgery-specific, with many programmes using preoperative risk models in an attempt to predict need for and length of stay within intensive care. Standardising postoperative ICU management can lead to reductions in length of stay with no increase to postoperative complications (Agarwal et al. 2012). Programmes within ICUs should consist of a multidisciplinary team who utilise a model of perioperative care components of enhancing recovery.

Physiotherapy within intensive care units

The aim of physiotherapy treatment provided within ICUs can be broadly separated into two: improving respiratory function, and initiating the rehabilitation process. Patients in an ICU may require mechanical ventilation to help their breathing; however this can lead to pulmonary complications. Respiratory physiotherapy involves early mobilisation where possible, repositioning patients within bed to optimise respiratory function, and utilising manual techniques or the manipulation of ventilator settings to clear lung secretions that build up within the lungs, when mobility and consequently deep breathing is limited. This helps to reduce the risk of pulmonary issues. Rehabilitation physiotherapy focuses initially on maintaining range of joint motion to prevent contractures, and on reducing the muscle loss that occurs due to immobility whilst a patient is in an ICU. Rehabilitation then focuses as soon as possible to sitting, standing and then walking, in order to facilitate their return to physical function. Patients can become weak quickly, and the use of exercises, electrical stimulation and ambulation practice can reduce muscle atrophy and joint stiffness that may occur.

> **An admission to ICU should therefore not mean that a patient is removed from an ERAS pathway**

The aforementioned roles of a physiotherapist within an ICU assimilate strongly with the key ERAS principles for accelerating the achievement of discharge criteria. To ensure a patient admitted to ICU continues to achieve functional recovery, the role of the physiotherapist is important. The impact of a perioperative ERAS programme has been shown to reduce the incidence of pulmonary complications with sustained improvement evident one year after implementation in patients admitted to an ICU following elective major surgery (Moore et al. 2017). Using an evidence-based physiotherapy protocol that addresses pulmonary dysfunction and promotes early mobility has been found to be safe and effective in comparison to non-specialist care for patients on ICU (Hanekom et al. 2013). An appropriate level of clinical expertise should be required to safely work in a critical care environment, and creating an algorithm to guide non-specialist therapists can encourage best practice physiotherapy (Sommers et al. 2015) promoted within ERAS guidelines.

Early mobilisation of critically ill patients in an ICU is a safe and effective intervention that may lead to significant improvements to functional outcomes (Adler and Malone 2012). An admission to ICU should therefore not mean that a patient is removed from an ERAS pathway. In fact, it may be argued that it is the ICU-admitted patients that need ERAS the most. Mobilising a patient can include activities such as sitting, standing, ambulation and passive exercises performed by the physiotherapist. Functional exercise capacity, self-perceived functional status and muscle force have been reported to be greater at hospital discharge for patients receiving a passive or active exercise training session for 20 minutes a day (Burtin et al. 2009). Early mobilisation has also been linked to a decrease in mechanical ventilation duration when a multidisciplinary team with a recognised leader can implement change to the ICU culture and practice (Hashem et al. 2016).

Barber and colleagues (2015) found barriers to early mobilisation within ICUs to be a lack of resources and communication; highlighting the importance of educating and including the ICU team within the traditional ERAS team of anaesthetists, surgeons, and ward-based nurses and allied health professionals. Education should include the clinical aspects as well as combined working to ensure logistical factors are coordinated, such as the use of standard documentation. For example, ERAS patients are often managed on a specific ERAS pathway document; this needs to work seamlessly with ICU pathway documentation.

Rehabilitation post discharge

Following a critical illness or prolonged stay in an ICU, patients may suffer from physical, psychological and cognitive problems, which can negatively impact their health-related quality of life (Jones 2012). Intensive care unit-acquired weakness (ICUAW) is a clinical syndrome that occurs due to muscle atrophy and loss of muscle mass whilst a patient is intubated and mechanically ventilated. Recovery time increases with length of stay, and an effective rehabilitation programme is vital to ensure a patient can return as close as possible to their preoperative physical and mental health.

Functional limitations and persistent weakness may exist long after discharge, and therefore there is a need to increase the awareness and involvement of physiotherapists within the outpatient setting (Pawlik and Kress 2013). Physiotherapists are an essential

component of the rehabilitation pathway, and can ensure that patients adopt ERAS principles, proven to facilitate recovery, once they are discharged from an ICU. The rehabilitation needs of a patient should be individualised, and assessments are important to determine which physiotherapy and counselling resources are required. Consequently, an adequate number of well-informed physiotherapists who are competent at managing critical care patients in an outpatient setting is needed.

There is limited evidence regarding the effectiveness of physiotherapy interventions following admission to an ICU, and ERAS guidelines for post-discharge rehabilitation are still evolving. Recent literature has suggested that high intensity rehabilitation could lead to greater improvements in functional outcomes in comparison to lower intensity programmes (Bandholm and Kehlet 2012). The use of progressive resistance training has been highlighted for augmenting a patient's hypertrophy, improving their strength, balance and muscular endurance (Borst 2004). Jones et al. (2003) found a self-help rehabilitation manual to be effective in aiding physical recovery and reducing depression; however, many patients still recalled delusional memories from ICU, prompting the need for further psychological care. A physiotherapy-led, outpatient rehabilitation programme, involving education sessions and circuit-based training has been proven to enhance exercise capacity along with significant psychological benefits following discharge from an ICU (McWilliams et al. 2009).

With this considered, a Cochrane review of exercise rehabilitation for recovery following discharge from an ICU was unable to determine an overall result for the effect of exercise training on recovery. Six studies were examined: three of the papers reported results in favour of post-discharge exercise training programmes and the remaining studies found no effect. Interventions included walking, strengthening exercises, education, arm and leg cycling exercises and self-help rehabilitation manuals (Connolly et al. 2015). Despite inconclusive results, the authors highlight the importance of physical rehabilitation for recovery after a critical illness.

Conclusion

The role of physiotherapy within ERAS and rehabilitation following intensive care is important and will be increasingly more so, as the development of ERAS programmes leads to a shift in outcome measures, from the current surrogate of length of stay, to functional and activity-based markers of recovery. There is limited research available that focuses on the effect of an ERAS programme on outcomes for patients discharged from an ICU following elective major surgery. This cohort may have the most to gain from a multimodal approach that integrates evidence-based interventions. Critical care physiotherapists adopt roles that assimilate strongly with key ERAS principles, and they can play a vital role in ensuring patients remain on track with their ERAS pathway whilst in an ICU. Providing a more intense, coordinated rehabilitation programme for patients following discharge from an ICU, delivered by a specialised physiotherapist and supported by a multidisciplinary team is hypothesised to improve recovery (Walsh et al. 2012).

Future research and investigation

Future research should focus on establishing a standardised rehabilitation programme, informed by ERAS principles, which can be delivered by specialist physiotherapists within an ICU and in an outpatient setting. Prospective studies are needed to determine the long-term effect of early mobilisation and exercise-based interventions. The ability to recover following discharge from an ICU can be more accurately measured when compared to values of baseline function, allowing clinicians to consider patients with pre-existing co-morbidities, who are less likely to respond to rehabilitation interventions. Thus, a safe and effective method for determining preoperative functional ability should be researched. Consideration of how to attain and importantly measure functional recovery should be the focus for physiotherapy research in the future, providing evidence for its inclusion in the ERAS programmes of tomorrow. ■

Abbreviations

ERAS enhanced recovery after surgery
ICU intensive care unit
ICUAW intensive care unit-acquired weakness

References

AbdelSalam H, Restrepo C, Tarity D et al. (2012) Predictors of intensive care unit admission after total joint arthroplasty. J Arthroplasty, 27(5): 720-725.

Adler J, Malone D. (2012) Early Mobilization in the intensive care unit: A systematic review. Cardiopulm Phys Ther J. 23(1): 5-13.

Agarwal HS, Saville BR, Slayton JM et al. (2012) Standardized postoperative handover process improves outcomes in the intensive care unit: A model for operational sustainability and improved team performance. Crit Care Med, 40(7): 2109-2115.

Bandolm T, Kehlet H. (2012) Physiotherapy exercise after fast-Track total hip and knee arthroplasty: Time for reconsideration? Arch Phys Med Rehabil. 93(7). 1292-1294.

Barber EA, Everard T, Holland AE et al. (2015) Barriers and facilitators to early mobilisation in intensive care: A qualitative study. Australian Critical Care, 28(4): 177-182.

Borst SE. (2004) Systematic Review: Interventions for sarcopenia and muscle weakness in older people. Age Ageing, 33: 548-555.

Burtin C, Clerckx B, Robbeets C et al. (2009). Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med, 37(9): 2499-2505.

Carli F, Charlebois P, Stein B et al. (2010) Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg, 97(8): 1187-1197.

Connolly B, Salisbury L, O'Neil B et al. (2015) Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev, 22(6): CD008632.

Epstein NE. (2014) A review article on the benefits of early mobilization following spinal surgery and other medical/surgical procedures. Surg Neurol Int, 5(Suppl 3): S66-S73.

ERAS Society (2017). ERAS Society Guidelines. Available from: http://erassociety.org/guidelines/list-of-guidelines/. [Accessed August 7 2017].

Hanekom S, Louw QA, Coetzee AR. (2013) Implementations of a protocol facilitates evidence-based physiotherapy practice in intensive care units. Physiotherapy 99(2): 139-145.

Hashem MD, Nelliot A, Needman DM. (2016) Early mobilization and rehabilitation in the ICU: Moving back to the future. Respiratory care, 61(7): 971-979.

Hoogeboom TJ, Donkers JJ, Hulzebos EH et al. (2014) Merits of exercise therapy before and after major surgery. Curr Opin Anaesthesiol, 27(2):161-166.

Jones C, Skirrow P, Griffiths RD et al. (2003). Rehabilitation after critical illness: A randomized, controlled trial. Crit. Care. Med. 31(10): 2456-2461.

Jones C. (2012) Surviving the intensive care: Residual physical, cognitive and emotional dysfunction. Thorac Surg Clin, 22(4): 509-516.

Kehlet H, Wilmore D. (2008) Evidence-based surgical care and the evolution of fast-track surgery. Annals of surgery, 248(2): 189-198.

McWilliams DJ, Atkinson D, Carter A et al. 2009. Feasibility and impact of a structured, exercise-based rehabilitation programme for intensive care survivors. Physiother Theory Practice, 25(8):566-571.

Moore JA, Conway DH, Thomas N et al. (2017) Impact of a perioperative quality improvement programme on postoperative pulmonary complications. Anaesthesia, 72(3): 317-327.

Paton F, Chambers D, Wilson P et al. (2014) Effectiveness and implementation of enhanced recovery after surgery programmes: a rapid evidence synthesis. BMJ Open, 4(7): e005015.

Pawlik AJ, Kress JP. (2013) Issues affecting the delivery of physical therapy services for individuals with critical illness. Phys Ther, 93(2): 256-265.

Sommers J, Engelbet RHH, Dettling-Ihnenfeldt D et al. (2015) Physiotherapy in the intensive care unit: an evidence-based, expert driven practical statement and rehabilitation recommendations. Clin Rehabil. 29(11): 1051-1063.

Walsh TS, Salisbury LG, Boyd J et al. 2012. A randomised controlled trial evaluating a rehabilitation complex intervention for patients following intensive care discharge: the RECOVER study. BMJ Open, 2:e001475.

Frederic Michard
Managing Director
MiCo
Denens, Switzerland

frederic.michard@bluewin.ch

@MichardFrederic

fredericmichard.wixsite.com/mico

Innovations in Monitoring

From Smartphones to Wearables

This article describes recent advances and perspectives in cardiorespiratory monitoring for surgical patients, from prehabilitation to rehabilitation, from smartphones to wearable sensors.

There are over 320 million inpatient surgical procedures worldwide (Weiser et al. 2015). We learnt from the recent International Surgical Outcomes (ISOS) Study (ISOS Group 2016) that around 17% of these patients develop one or more complications, and among them, that 2.8% die from their complications. One can therefore estimate that around 1.5 million patients/yr (4500 patients/day or 3 patients/min) die of postoperative complications. In the USA, if postoperative mortality was part of the official statistics from the Centers for Disease Control and Prevention, it would represent the third leading cause of death, right after cancer (Bartels et al. 2013). Postoperative complications are not only a human burden. They also dramatically increase hospital costs (Michard et al. 2015).

Facing this clinical and economic burden, several initiatives have been developed to improve quality of surgical care, from the Surgical Safety Checklist, to minimally-invasive surgery, protective mechanical ventilation, and enhanced recovery programmes. Thanks to technological innovations, closer, better and easier monitoring of patients undergoing surgery may also help to improve outcome. Recent advances and perspectives in cardiorespiratory monitoring will be discussed here, from prehabilitation to rehabilitation.

Prehabilitation

Prehabilitation is known to have an impact on postoperative outcome. Preoperative change in physical status and a better control of risk factors can be facilitated by digital tools and applications (apps) downloaded on smartphones or tablets. Connected devices such as wireless brachial cuffs and electronic scales can be used for self-monitoring of blood pressure and weight, the visualisation of trends over time, and a better control of hypertension and overweight before surgery (Michard et al. 2017a). Digital games have been developed for smoking cessation, and multiple activity trackers and apps now exist to invite patients to monitor and increase their physical activity. These digital tools seem to be effective only for a short period of time, which is clearly an issue when dealing with chronic conditions and diseases, but less of a problem if used during the few weeks preceding surgery (Michard et al. 2017a).

Intraoperative management

Fluid management

Intraoperative fluid management is a key determinant of postoperative outcome. Fluid overload has been known for a while as responsible for complications related to tissue oedema (e.g. anastomotic leak, prolonged mechanical ventilation), so that fluid restriction has been encouraged at some point. However, recent studies have clearly demonstrated that insufficient fluid administration is also associated with a significant increase in postoperative complications (Thacker et al. 2016). Therefore titrating or tailoring fluid administration to individual needs is highly desirable to ensure patients receive the right amount of fluid at the right time. Multiple noninvasive haemodynamic monitoring solutions are now available, from bioimpedance tracheal tubes, to bioreactance surface electrodes, applanation tonometry and volume clamp methods (Michard et al 2017a). They give clinicians the opportunity to measure and track changes in blood flow during therapeutic interventions and to rationalise fluid administration. Preventing unjustified fluid administration by detecting fluid unresponsiveness has been shown to be useful to decrease postoperative morbidity, hospital length of stay and costs (Benes et al. 2014; Michard et al. 2017b). Noninvasive parameters such as the pleth variability index (PVI) from pulse oximeters and pulse pressure variation (PPV) from volume clamp methods are useful to detect fluid unresponsiveness.

Blood pressure management

A strong relationship has been established between intraoperative hypotension and postoperative complications, such as stroke, myocardial and acute kidney injury. Intermittent blood pressure measurements do not allow capture of all hypotensive events in a timely manner. Studies suggest that we may miss around 7 minutes of hypotension per hour during typical 3-hour abdominal and orthopaedic procedures when using intermittent measures of blood pressure from a brachial cuff (Chen et al. 2012). It has recently been suggested that only a few minutes of hypotension are susceptible to affect postoperative outcome (Salmasi et al. 2017). Therefore, although causality between intraoperative hypotension and postoperative complications has not yet been established, it seems reasonable to avoid hypotension as much as we can. This may require a more rational and controlled use of anaesthetic agents, in particular during induction, as well as the continuous monitoring of blood pressure with noninvasive techniques for the immediate detection and correction of any significant blood pressure drop.

Blood management

An app has been developed to quantify blood loss in surgical sponges just by taking a picture of them. First studies suggest it works better than methods currently used for surgical blood loss estimation (Konig et al. 2017). Although measuring absolute values of haemoglobin noninvasively remains a challenge, tracking changes over time is now doable with an accept-

able level of accuracy (Marques et al. 2015). These new methods may help to rationalise blood transfusion and decrease associated complications.

Postoperative management

Recent studies have shown that around one-third of deaths after surgery occur in the wards (ISOS Group 2016). This situation has been called "failure to rescue", and has been proposed to explain why hospitals with comparable postoperative morbidity rates may have very different mortality rates: outcome depends more on the ability to detect early and treat properly postoperative complications than in the occurence of complications (Ghaferi et al. 2009). Importantly, many studies have shown that most ward patients start deteriorating hours before medical teams are called for rescue or intensive care unit (ICU) transfer. In this regard, several studies have already demonstrated the value of early detection with continuous monitoring systems.

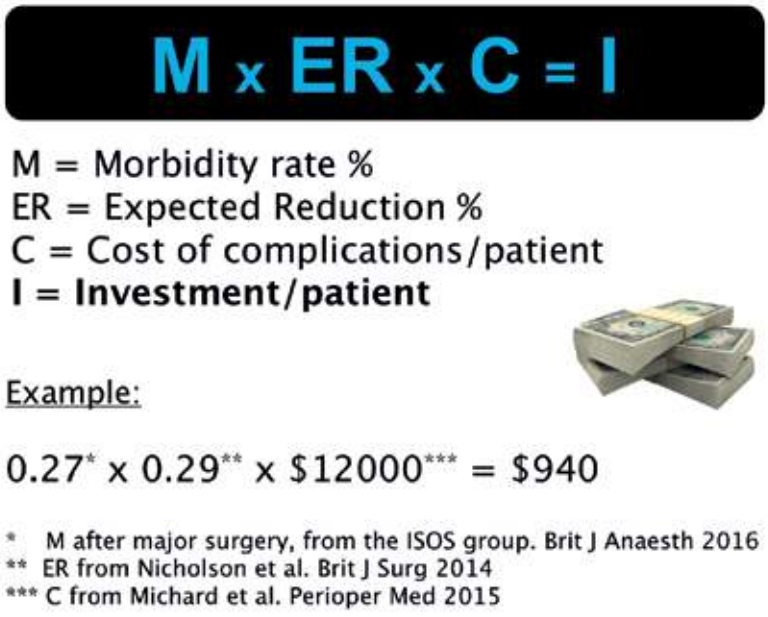


Figure 1. The MERCI equation
A simple equation to estimate how much hospitals can invest to improve quality of surgical care at no cost.

> "cost must be balanced with potential savings associated with expected improvement in postoperative recovery"

The use of pulse oximeters to continuously monitor SpO_2 and heart rate in 2,841 orthopaedic patients (many of them receiving opioids) was associated with a significant decrease in the number of rescue events and ICU transfers (Taenzer et al. 2010). The use of a piezoelectric contact-free sensor (placed under the mattress) to continuously monitor heart rate and respiratory rate in 2,314 medico-surgical patients was associated with a significant decrease in the number of calls for cardiac arrest and hospital length of stay (Brown et al. 2014). More recently, the use of wireless sensors to monitor vital signs (SpO_2, heart rate, blood pressure, respiratory rate), automatically calculate an early warning score and alert nurses in case of deterioration, was associated with a significant decrease in the number of cardiac arrests and in mortality (Subbe et al. 2017).

Multiple sensors and monitoring systems are now available for proactive monitoring in ambulatory patients (Michard et al. 2017a). Smart software has been developed to filter artifacts and prevent alarm fatigue, to fuse vital signs into wellness indexes or warning scores, which are used for the easy and visual detection of clinical deterioration, or even the prediction of adverse events beforehand (Michard et al. 2017c; Pinsky et al. 2016).

Rehabilitation

Activity trackers

Early mobilisation is a key element of postoperative recovery. Multiple wrist, waist or ankle sensors with accelerometers and gyroscopes are available to detect movement or body posture, and hence quantify physical activity. Some have been used with success for the objective assessment of early mobilisation. However, some are not sensitive enough to be used during low-speed exercises, which is often the case immediately after surgery (Michard et al. 2017a).

Electronic checklists

These are apps developed to optimise communication between patients and healthcare professionals during the entire surgical journey. Before surgery they can be used to ensure patients follow preoperative recommendations, in particular regarding medications. After surgery, and once patients have been discharged from the hospital, they can help to detect and describe complications (e.g., wound pictures can be shared) and provide guidance to patients.

Economic impact of technological innovations

The use and implementation of any new technology has a cost that must be balanced with potential savings associated with the expected improvement in postoperative recovery. Postoperative complications are expensive to treat, and prolong hospital length of stay (increase in hospital cost), reducing opportunities to free beds for new surgeries (decrease in hospital revenues). The MERCI equation has been proposed to simply and quickly estimate how much hospitals could invest to improve quality of surgical care at no cost (Michard 2016a). In this equation, M is the morbidity rate (or proportion of patients who develop at least one postoperative complication), ER is the expected reduction in postoperative morbidity with the new strategy to be implemented, C is the cost difference between patients with

Figure 2. Futuristic ring for monitoring in ambulatory patients

Today, all parameters listed in the figure can already be monitored noninvasively and continuously by various sensors and technologies. The integration and miniaturisation is only a matter of time and the clinical need is obvious.

RR respiratory rate SpO_2 arterial oxygen saturation PR pulse rate PRV pulse rate variability (arrhythmia detection) BP blood pressure BFlow blood flow or cardiac output Hb haemoglobin Temp temperature

and without complications. Then, I gives an estimate of the possible investment to decrease postoperative morbidity at no cost (**Figure 1**). According to a recent systematic review and meta-analysis, enhanced recovery programmes are capable of decreasing postoperative complications by around 29% (Nicholson et al. 2014). The large International Surgical Outcomes Study (ISOS Group 2016) suggests that the average postoperative morbidity rate of patients undergoing major surgery is 27%, and we know from another recent study (Michard et al. 2015) that the average cost of complications per patient is around US$12,000. In this major surgery context, the MERCI equation shows that the maximum investment per patient (to improve quality of care at no cost) is around $940 (**Figure 1**). This is a significant amount of money, but it will not allow the purchase and implementation of all technologies described in this article. When investing in new monitoring equipment, assuming an outcome benefit has been demonstrated or is suspected, the MERCI equation helps to build a business case and define priorities.

Looking forward: all in one

Thanks to computer science and bioengineering innovations, monitoring systems will continue to evolve quickly. Stretchable and flexible electronics enable the measurement of blood pressure with tiny and inexpensive sensors made of materials "feeling" our pulse (Michard 2016b). When positioned on radial and carotid arteries, these sensors record and transmit wirelessly high-quality blood pressure curves to any display, from a large screen to a watch. If used in combination with pulse contour algorithms, they will open the door to the remote and ambulatory monitoring of advanced haemodynamic parameters (Michard 2016b). Other variables, such as arterial oxygen saturation, respiratory rate, haemoglobin, temperature and activity can already be monitored noninvasively and continuously. Therefore, it is only a matter of time before all these physiologic variables are integrated into the same sensor or monitoring system (**Figure 2**).

Conclusion

Postoperative complications are a major clinical and economic burden. Each year, they are responsible for over 1 million deaths. Many complications and deaths could be prevented with better pre- and intraoperative management, the earlier detection of adverse events and more informed therapeutic decisions. The digital revolution is transforming medicine, and physiologic monitoring should dramatically benefit from ongoing hardware and software innovations. New and future monitoring tools have the potential to help us improve quality of surgical care from prehabilitation to rehabilitation. In particular, wireless and wearable sensors can help to detect clinical deterioration at a very early stage in ward patients. By triggering timely interventions, they have the potential to decrease the number of ICU admissions, cardiac arrests and postoperative deaths. The next chapter of physiologic monitoring might be written beyond the operating room and the ICU. ■

Conflict of interest

Frederic Michard is the founder and managing director of MiCo, a Swiss consulting firm providing services to medtech companies, digital health startups and life science investors.

References

Bartels K, Karhausen J, Clambey ET et al. (2013) Perioperative organ injury. Anesthesiology, 119: 1474-89.

Benes J, Giglio MT, Brienza N, Michard F (2014) The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. Crit Care, 18: 584.

Brown H, Terrence J, Vasquez P et al. (2014) Continuous monitoring in an inpatient medical-surgical unit: a controlled clinical trial. Am J Med, 127: 226-32.

Chen G, Chung E, Meng L et al. (2012) Impact of non-invasive and beat-to-beat arterial pressure monitoring on intraoperative hemodynamic management. J Clin Monit Comput, 26: 133-40.

Ghaferi AA, Birkmeyer JD, Dimick JB (2009) Variation in hospital mortality associated with inpatient surgery. N Engl J Med, 361: 1368-75.

Konig G, Waters JH, Javidroozi M et al. (2017) Real-time evaluation of an image analysis system for monitoring surgical hemoglobin loss. J Clin Monit Comput, Apr 7. doi: 10.1007/s10877-017-0016-0.

Marques NR, Kramer GC, Voigt RB et al. (2015) Trending, accuracy, and precision of non-invasive hemoglobin monitoring during human hemorrhage and fixed crystalloid bolus. Shock, 44(Suppl1): 45-9.

Michard F, Mountford WK, Krukas MR et al. (2015) Potential return on investment for implementation of perioperative goal directed fluid therapy in major surgery: A nationwide database study. Perioper Med, 4:11.

Michard F (2016a) MERCI for improving quality of surgical care at no cost. World J Surg, 40: 3095-6.

Michard F (2016b) Hemodynamic monitoring in the era of digital health. Ann Intensive Care, 6: 15.

For full references, please email editorial@icu management.org or visithttps://iii.hm/ddv

Edwards upcoming events

Join us at ESICM in Vienna for our
Lunch Symposium

Novel Strategies to Optimize Perioperative Monitoring

Edwards Lunch Symposium
Tuesday, September 26
12.30-14.00
ESICM, Room Berlin (level 0)

Moderators:

Monty Mythen (London, UK)
Thomas Scheeren (Groningen, The Netherlands)

Speakers:

Frederic Michard (Lausanne, Switzerland)
New aspects of fluid responsiveness assessment

Daniel Sessler (Cleveland, USA)
Why hypotension matters?

Denise Veelo (Amsterdam, The Netherlands)
Predicting hypotension in 2017: from reactive to proactive clinical decisions

Monty Mythen (London, UK)
Fluid therapy in the perioperative setting

Jean-Louis Vincent (Brussels, Belgium)
The role of continuous PAC in today's ICU

Visit stand 510 or register on www.edwards.com/gb/ESICM2017

Meet us online for our
Virtual Symposium

The Future of Anesthesia - Predictive Monitoring

Edwards Virtual Symposium
Thursday, October 5
Start at 18.00 (Paris time)
www.edwardsESRsymposium.com

Speakers:

Marco Ranucci (Milan, Italy)
The future of medicine with Big Data and Machine Learning

Daniel Sessler (Cleveland, USA)
The importance of hypotension

Bart Geerts (Amsterdam, The Netherlands)
Predicting hypotension in 2017: from reactive to proactive clinical decisions

Followed by 30 minutes live interaction with the experts

Register and follow the symposium on www.edwardsESRsymposium.com

Edwards Lifesciences • Route de L'Etraz 70, 1260 Nyon, Switzerland • edwards.com

Edwards

Carrie M. Goodson
Fellow
Johns Hopkins University School of Medicine
Outcomes After Critical Illness and Surgery (OACIS) Group
Division of Pulmonary & Critical Care Medicine
Baltimore, MD, USA

cgoodso1@jhmi.edu

@carriemgoodson

Claire Tipping
Physiotherapist
Physiotherapy Department
Alfred Hospital
Melbourne, Australia
PhD Candidate
School of Public Health and Preventive Medicine
Monash University
Melbourne, Australia

c.tipping@alfred.org.au

Earl C. Mantheiy
Senior Clinical Program Coordinator, Johns Hopkins University School of Medicine, Outcomes After Critical Illness and Surgery (OACIS) Group, Division of Pulmonary & Critical Care Medicine
Baltimore, MD, USA

Dex@jhu.edu

Sina Nikayin
Research Program Assistant, Johns Hopkins University School of Medicine, Outcomes After Critical Illness and Surgery (OACIS) Group, Division of Pulmonary & Critical Care Medicine
Baltimore, MD, USA

sina.nikayin@jhmi.edu

Jason Seltzer
Physical Therapist, ICU Team Coordinator. Department of Physical Medicine & Rehabilitation, Johns Hopkins Hospital, Baltimore, MD USA

Jseltze5@jhmi.edu

Caroline Outten
Nurse Clinician, Medical Intensive Care Unit, Johns Hopkins Hospital, Baltimore, MD, USA

coutten2@jhmi.edu

Biren B. Kamdar
Assistant Professor, David Geffen School of Medicine
Division of Pulmonary and Critical Care Medicine
University of California, Los Angeles, CA, USA

bkamdar@mednet.ucla.edu

@BirenKamdar

Dale M. Needham
Professor, Johns Hopkins University School of Medicine
Outcomes After Critical Illness and Surgery (OACIS) Group
Division of Pulmonary & Critical Care Medicine and Department of Physical & Rehabilitative Medicine
Baltimore, MD, USA

dale.needham@jhmi.edu

@DrDaleNeedham

Physical rehabilitation in the ICU

Understanding the evidence

Reviews the latest evidence evaluating physical rehabilitation in the intensive care unit setting and future directions for the field.

Survivors of critical illness frequently experience poor physical outcomes, including persistent impairments in muscle strength, exercise capacity and physical function (Pfoh et al. 2016; Herridge et al. 2011; Dinglas et al. 2017; Fan et al. 2014b). In this article, we review these impairments and recent clinical trials evaluating physical rehabilitation during critical illness as a potential means to improve these outcomes, and conclude with considerations for future studies in the field (**Figure 1**).

Background: what is intensive care unit (ICU)-acquired weakness?

ICU-acquired weakness (ICUAW) is a syndrome of diffuse and symmetric muscle weakness for which no cause other than critical illness can be found (Stevens et al. 2009). Weakness is defined based on physical examination of muscle strength, in an alert and cooperative patient, using the Medical Research Council (MRC) scale. A MRC sum score of <48 (range: 0-60, maximum = 60) is consistent with ICUAW.

Muscle weakness consistent with ICUAW occurs in 11% of all patients admitted to an ICU for ≥1 day (Nanas et al. 2008), with a higher prevalence of 26-65% in patients mechanically ventilated for ≥5 days (Ali et al. 2008; Sharshar et al. 2009; Dinglas et al. 2017). Loss of muscle mass occurs quickly during critical illness. Compared to the day of ICU admission, cross-sectional area of the rectus femoris muscle decreased by 18% at day 10, with necrosis seen in 54% of muscle biopsies (Puthucheary et al. 2013).

Patients with ICUAW experience worse in-hospital and post-hospitalisation outcomes. Among patients requiring mechanical ventilation for ≥5 days, ICUAW is associated with a 2-fold increase in duration of mechanical ventilation (De Jonghe et al. 2002; Ali et al. 2008), and a 2- to 5-fold increased hospital mortality (Sharshar et al. 2009; Ali et al. 2008). One-year mortality almost doubled in a propensity-matched analysis of patients with vs. without ICUAW (30.6% vs. 17.2%, p = 0.015) (Hermans et al. 2014). Two years after surviving ICU admission for acute respiratory distress syndrome (ARDS), patients with ICUAW achieved only 40% of predicted 6-minute walk distance vs. 60% in those without ICUAW (p <0.01) (Fan et al. 2014b). In the same cohort, patients with vs. without ICUAW demonstrated decreased quality of life (QOL) two years after ARDS (30% vs. 70% of population normative scores on the Short Form 36 Health Survey (SF-36) physical function subscale, p < 0.001) (Fan et al. 2014b). Post-discharge survival over 5 years after ARDS was significantly worse in patients with ICUAW (Dinglas et al. 2017).

Pathology

ICUAW encompasses a variety of muscle and nerve disorders, which may overlap, including critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and disuse atrophy (Stevens et al. 2009). CIP is defined as ICUAW with electrophysiological evidence of a sensorimotor axonal polyneuropathy; CIM is ICUAW with myopathic features on muscle biopsy or electromyography (EMG, recorded during voluntary muscle contraction). CIP and CIM frequently coexist, given common risk factors and potential mediators (Stevens et al. 2009). Pathophysiologically, CIP and CIM are associated with increased inflammatory markers, and microcirculatory and metabolic impairments that are also associated with multi-organ dysfunction syndrome (Batt et al. 2013; Witteveen et al. 2017).

Risk factors

Multiple studies have evaluated patient- and ICU-related risk factors for ICUAW. Older age, immobility, sedation, sepsis, multi-organ fail-

ure, hyperglycaemia and mechanical ventilation are consistently reported risk factors for ICUAW (Fan et al. 2014a; Puthucheary et al. 2012; Hermans and Van den Berghe 2015; de Jonghe et al. 2009). The most readily modifiable risk factors are immobility, sedation and hyperglycaemia. Steroids and neuromuscular blocking agents have been reported as risk factors (Hermans and Van den Berghe 2015; Needham et al. 2014), but a causal association is not certain (Puthucheary et al. 2012), given that immobilisation and sedation are confounders in most analyses (deBacker et al. 2017; Fan et al. 2014b). While difficult to evaluate in ICU patients, pre-ICU physical status appears to be an important factor for ICUAW and should be considered when evaluating a patient's risk for ICUAW (Batt et al. 2013; Latronico et al. 2017; Puthucheary and Denehy, 2015).

"There is emerging evidence demonstrating the benefit of earlier vs. later initiation of rehabilitation in the ICU"

Evidence: clinical trials evaluating physical rehabilitation in the ICU

Strength and physical function

The most direct effects of physical rehabilitation in the ICU may be on strength and physical functioning. A recent meta-analysis reported a significant improvement in muscle strength, measured by the MRC sum score, at ICU discharge (pooled mean difference 8.6, 95% CI 1.4-15.9, p = 0.02) and increased probability of walking without assistance at hospital discharge (OR 2.1, 95% CI 1.2-3.8, p=0.01) in rehabilitation intervention vs. control groups (Tipping et al. 2017). Growing evidence suggests that these improvements in strength and physical function may be greater when rehabilitation is initiated earlier. For instance, a randomised controlled trial (RCT) of physical and occupational therapy (PT, OT) interventions, started at a median of 1.5 days after intubation, vs. usual care (with PT and OT started at a median of 7.4 days after intubation) significantly increased return to independent functional status and walking at hospital discharge (59% vs. 35%, p = 0.02) (Schweickert et al. 2009). Similarly, two additional trials of early goal-directed mobilisation vs. usual care reported a doubling of the proportion of patients walking by ICU discharge (Hodgson et al. 2016; Schaller et al. 2016). By contrast, a RCT of more vs. less intensive PT interventions, beginning a median of 8 days after intubation, found no difference in functional status at 28 days (Moss et al. 2015).

Delirium

Several randomised trials have demonstrated an improvement in delirium with rehabilitation in the ICU. Early intervention by PT and OT, delivered during daily sedation interruption, resulted in a 50% decrease in delirium duration compared to very similar sedation (i.e., daily sedation interruption) with usual care rehabilitation therapy (Schweickert et al. 2009). ICU delirium-free days by day 28 increased by 3 days in patients managed with early, goal-directed mobilisation vs. usual care (Schaller et al. 2016). Notably, there was no difference in delirium incidence or duration in a RCT of standardised rehabilitation therapy vs. usual care where there was no sedation protocol and sedation levels that commonly prohibited active physical therapy interventions, which may have contributed to the lack of benefit (Morris et al. 2016). A RCT evaluating interventions led by OT (without additional PT involvement) vs. usual care, reported a dramatic decrease in delirium incidence from 20% to 3% in non-mechanically ventilated patients (Álvarez et al. 2017). Finally, pre-post evaluations of quality improvement bundles, including combined sedation and rehabilitation interventions, have resulted in marked reductions in delirium, although it is impossible to isolate the effect of the rehabilitation component in these studies (Balas et al. 2014; Needham and Korupolu 2010; Smith and Grami 2016).

Duration of mechanical ventilation and length of stay

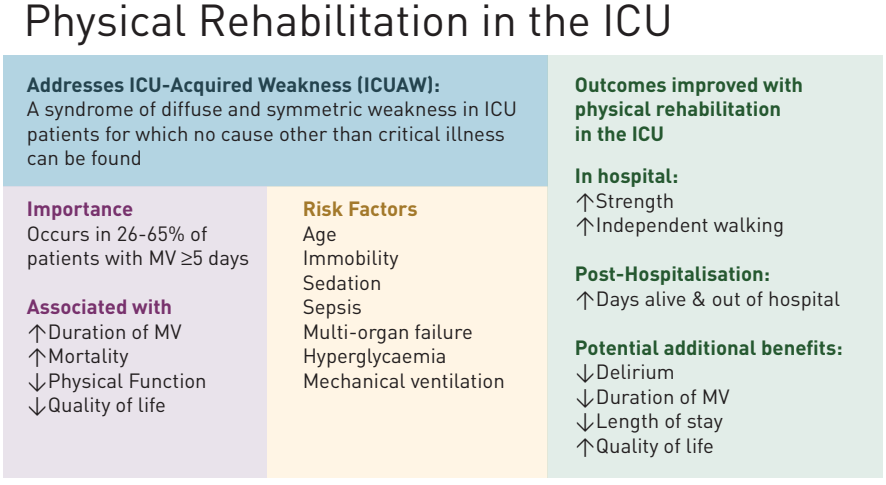
In a recent systematic review, 3 of 11 RCTs reported significant 1.7-5.8 day decreases in duration of mechanical ventilation (Schweickert et al. 2009; Dong et al. 2016; Dong et al. 2014). Of 13 studies that evaluated ICU length of stay, 10 reported decreases (Tipping et al. 2017), but only 2 reported data that were not potentially confounded by mortality. These studies both found significant reductions of 2.5-5.1 ICU days in intervention vs. control groups ($p < 0.05$) (Yosef-Brauner et al. 2015; Dong et al. 2014).

Mortality and post-discharge status

There is no difference in mortality at ICU discharge, hospital discharge, or 6-month follow-up in existing RCTs. However, "days alive and out of the hospital at 6 months" were significantly greater with rehabilitation vs. standard care in a recent meta-analysis (mean difference 9.63 days, 95% CI 1.68–17.57, p=0.02) (Tipping et al. 2017).

Quality of life

Physical function and role physical are 2 domains of the SF-36 QOL survey. No differences were seen in these domains at 6 months after ICU admission, although differences were seen in patient subgroups. Early rehabilitation (within



Abbreviations ICU = Intensive Care Unit; MV=Mechanical Ventilation

Figure 1. Summary of evidence on the importance and outcomes of physical rehabilitation in the ICU

3 days of ICU admission, 1 study) vs. control group increased the SF-36 physical function domain score (mean difference 22 points, p = 0.04) (Kayambu et al. 2013); late rehabilitation (2 studies) vs. control groups was not different (Tipping et al. 2017). The SF-36 role physical domain improved with high-dose (>30 minutes active rehabilitation daily, 2 studies) vs. control groups (mean difference 31 points, p = 0.001); low-dose rehabilitation (1 study) vs. control group was not different (Tipping et al. 2017).

Safety

Physical rehabilitation of critically ill patients (**Figure 2**) is safe (Tipping et al. 2017; Nydahl et al. 2017). A large systematic review of 22,351 mobilisation sessions delivered in 7,546 ICU patients, from a combination of observational and clinical trials, demonstrated a rare frequency of events. Potential safety events, defined as a clinical deterioration or event exceeding a study's safety limit, occurred in only 2.6% of sessions. Events of consequence, defined as being events associated with cessation of a mobility session, adverse health consequence or requirement of additional therapy, occurred in only 0.6% of sessions. Most potential safety events involved a haemodynamic change or oxygen desaturation that resolved with pause or cessation of mobility. Notably, removal of medical devices and falls were rare, including dysfunction or removal of an intravascular catheter (0.2% of sessions), endotracheal tube removal (0.01%) and falls (0.07%) (Nydahl et al. 2017).

Future directions

The most pressing questions for consideration in future studies in the field include the optimal type and dose of rehabilitation interventions, timing of initiation of intervention and ICU patient sub-populations (Denehy et al. 2017). While PTs may mobilise patients to a higher level than nurses (Garzon-Serrano et al. 2011), nurses can provide clinically beneficial mobility interventions, as clearly demonstrated in a recent RCT (Schaller et al. 2016). There are many types of interventions to be considered in future studies, including functional mobility, strengthening and use of relevant technology and equipment (e.g., in-bed cycle ergometry, neuromuscular electrical stimulation, tilt tables, interactive video games, hydrotherapy), along with consideration of potentially synergistic interventions with rehabilitation, such as nutritional supplementation (Needham et al. 2009; Sommers et al. 2017; Arabi et al. 2017; Heyland et al. 2015).

There is emerging evidence demonstrating the benefit of earlier vs. later initiation of rehabilitation in the ICU, which should be considered when designing future trials and implementing rehabilitation as part of clinical practice in the ICU. Most studies have had broad eligibility criteria, but it is possible that patients' pre-ICU baseline status (e.g., frailty and comorbidity) or ICU-based diagnosis (e.g., sepsis) may better identify patients who are most likely to benefit from rehabilitation (Puthucheary and Denehy 2015).

Finally, more fully understanding the effects of ICU-based rehabilitation is limited by heterogeneity in reporting among the published reports. Future studies should adopt standardised reporting methods of intervention, potential safety events and outcome measures, including separately reporting outcomes for survivors and non-survivors where appropriate (Hoffmann et al. 2014; Slade et al. 2016; Connolly et al. 2017; Needham et al. 2017).

Conclusions

Muscle wasting and weakness commonly develops within days of ICU admission, with effects on survival and physical functioning lasting for years post-discharge. Early-onset physical rehabilitation is a safe intervention in ICU patients that, based on existing RCTs, improves strength and physical functioning, and may improve delirium in the ICU as well as in-hospital and post-hospitalisation healthcare resource utilisation. ■

Figure 2. Mechanically-ventilated patient ambulating in the intensive care unit

Conflict of interest

Dale M. Needham is a principal investigator on a NIH-funded multi-site randomised trial evaluating nutrition and exercise in acute respiratory failure and, related to this trial, is currently in receipt of an unrestricted research grant and donated amino acid product from Baxter Healthcare Corporation and an equipment loan from Reck Medical Device. The other authors declare that they have no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome
CIM critical illness myopathy
CIP critical illness polyneuropathy
EMG electromyography
ICU intensive care unit
ICUAW intensive care unit-acquired weakness
MRC Medical Research Council
OT occupational therapy
PT physical therapy
QOL quality of life
RCT randomised controlled trial
SF-36 Short Form 36 Health Survey

References

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

See and deliver
what the patient wants

NAVA
Personalized ventilation

Scan QR code for more info about NAVA personalized ventilation and our Servo ventilators.

www.getinge.com

GETINGE

This document is intended to provide information to an international audience outside of the US.

Paul E. Wischmeyer
Professor of Anesthesiology and Surgery
Perioperative Research Director
Duke Clinical Research Institute
Department of Anesthesiology and Surgery
Duke University School of Medicine
Durham, NC, USA

Paul.Wischmeyer@Duke.edu

@Paul_Wischmeyer

Optimising nutrition for recovery after ICU

Optimising nutrition and metabolism post-ICU for recovery of functional lean body mass and quality of life.

In-hospital mortality following intensive care unit (ICU) care has consistently declined in recent years (Kaukonen et al. 2014). However, these data reveal many of these ICU "survivors" are not returning home to functional lives after the ICU, but instead to rehabilitation and nursing home settings where it is unclear if they ever returned to a meaningful quality of life (QoL). As in-hospital ICU mortality has declined, we have markedly increased the number of patients going to rehabilitation settings (Kaukonen et al. 2014). Once in rehabilitation, it is unclear if these ICU "survivors" ever return home as we know; ~40% of mortality within the first year of ICU stay occurs post-ICU discharge (Weycker et al. 2003). Unfortunately for those who do survive, nearly half the survivors will not return to work in the first year following discharge (Kamdar et al. 2017), often as a result of post-intensive care syndrome (PICS) and weakness post-ICU (Dinglas et al. 2017).

PICS is a multi-factorial syndrome; however, a significant component of PICS is often post-ICU weakness. This is unfortunately not surprising as we know critically ill burn patients lose as much as a kilogram of lean body mass (LBM) per day (Stanojcic et al. 2016). Other ICU patients also suffer significant LBM loss, much of it in the first 7-10 days of ICU stay (Wischmeyer 2016). Patients gain weight back following the ICU, but virtually all this regained weight is fat mass, not functional muscle and LBM (Herridge et al. 2003). This is not surprising, as data from the burned ICU patients demonstrates the catabolic/hypermetabolic state brought on by critical illness can persist for up to two years following hospital discharge and markedly hinders recovery of QoL, muscle mass and function in our ICU patients (Stanojcic et al. 2016).

To address this epidemic, we must ask ourselves in our ICU care, "Are we creating survivors or victims?" If we are going to begin creating more survivors we must improve our post-ICU care "recovery" care and take responsibility for the deficits in strength, function, and cognition we create in the ICU. We owe it to our ICU patients to optimise and further study key recovery interventions such as nutrition delivery post-ICU if we are to end the epidemic of PICS victims.

Metabolism and caloric needs for recovery after ICU

As patients improve and enter the "recovery phase", seminal ICU metabolic cart data and landmark studies of starvation indicate caloric and protein intake needs to increase significantly (Uehara et al. 1999; Keys et al. 1950; Hoffer and Bistrian 2012). This should occur concurrently with implementation of aggressive rehabilitation and exercise interventions. Data from the landmark "Minnesota Starvation Study", performed at the end of World War II (Kalm and Semba 2005; Keys et al. 1950) (a study all medical students and ICU caregivers should be taught or read themselves) provides fundamental data on the nutritional targets required to recover from the fundamental severe LBM loss observed after ICU. This seminal study demonstrates a healthy 70 kg human, following a significant weight loss, requires *an average of 5000 kcal/day for 6 months–2 years to fully regain lost muscle mass and weight* (Keys et al. 1950). Most all ICU and major surgery patients suffer similar marked weight and LBM loss. However, in addition to this significant LBM loss, ICU survivors also suffer prolonged hypermetabolism and catabolism (which Minnesota subjects did not have as they were healthy volunteers). Thus, we must consider this additional challenge to recovery of functional LBM, and again emphasise significant calorie/protein delivery will be required to restore lost muscle mass and QoL. ICU metabolic cart studies demonstrate during the recovery phase post-ICU, the body has a marked increase in metabolic needs, with total energy expenditure (TEE) increasing as much as ~1.7-fold above resting energy expenditure (REE) (Uehara et al. 1999). In the 2nd week following sepsis this reveals caloric need (TEE) of ~3250 kcal/d or 47 kcal/kg/d. Interestingly this is virtually identical to WHO requirements for normal, healthy humans to maintain weight. In younger trauma patients (mean age: 34), this data indicated an even greater increase in caloric need (TEE) in the 2nd week post-injury to *~4120 kcal/d or 59 kcal/kg/d*, nearly identical to the 4000 kcal/d Dr. Ansel Keys showed was required to recover from starvation in young subjects in the Minnesota study. Further, need for additional protein intake has been well-described by our research group and Hoffer et al. in a number of recent publications questioning whether it is actually protein deficit and not calorie deficit that is important to improving outcome in critical illness (Hoffer and Bistrian 2012; 2014; 2015) .This data demands we ask: *Is it possible our septic patients have been unable to recover their QoL post-ICU for months to years (Needham et al. 2011; Wischmeyer and San-Millan 2015; Kamdar et al. 2017; Dinglas et al. 2017) due to our lack of understanding of their fundamental metabolic needs in different phases of illness, especially following ICU and hospital discharge?*

How to optimise nutrition delivery after ICU for recovery

We must ask ourselves: *"Will patients leaving*

our ICU be able to consume adequate calories and protein to optimally recover?" Unfortunately, in most cases the answer is a resounding no!... At least not without help. Recovering patients, especially elderly individuals, are challenged by decreased appetites, persistent nausea and constipation from opiates, and lack of education about how to optimise their diet. Further, dysphagia following ICU stay occurs in nearly 60% of patients who are intubated in ICUs after extubation, and approximately 50% of these suffer from aspiration (Brodsky et al. 2017). Recent data has shown these dysphagia symptoms persist beyond hospital discharge in one-third of intubated ARDS survivors (Brodsky et al. 2017). Dysphagia must be actively assessed for and treated in ICU survivors. Thus, many challenges exist to recovery of oral intake post-ICU discharge. Actual post-ICU oral caloric intake has been explored in ICU patients in the week following extubation. An observational study demonstrated an average spontaneous calorie intake of 700kcal/d and the entire population studied consumed < 50% of calorie/protein needs for 7 days (Peterson et al. 2010). These data emphasise the importance of closely observing food intake in post-ICU patients.

Given these data and the many challenges to oral intake, patients following ICU discharge are highly unlikely to take in the required calorie and protein delivery for recovery via routine oral intake. *To address this, a large body of data demonstrates that oral nutrition supplements (ONS) must become fundamental in our post-ICU and hospital discharge care.* A recent meta-analysis in a wide range of hospitalised patients demonstrated ONS reduce mortality, reduce hospital complications, reduce hospital readmissions, shorten length of stay and reduce hospital costs (Cawood et al. 2012; Elia et al. 2016; Stratton et al. 2013; 2003). A large hospital database analysis of ONS use in 724,000 patients matched with controls not receiving ONS showed a 21% reduction in hospital LOS and for every US$1 spent on ONS $52.63 was saved in hospital costs (Philipson et al. 2013). Finally, a recent large post-hospital discharge randomised controlled trial of 652 patients in 78 centres studied the effect of high protein ONS (HP-ONS) with β-Hydroxy β-Methylbutyrate (HP-HMB) versus placebo ONS in elderly malnourished (Subjective Global Assessment [SGA] class B or C) hospitalised adults for 90 days following hospital discharge. Results demonstrated that HP-HMB reduced 90-day mortality ~50% relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90; p = 0.018). The number needed to treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4) (Deutz et al. 2016). As it is well known that patients recovering from sepsis and the ICU will not consume sufficient calories and protein to recover optimally, the use of HP-ONS will be essential and is strongly recommended for all patients once oral intake is resumed for at least 3 months (up to 1 year) following ICU.

Nutrition and metabolic support Post-ICU Discharge

Nutrition - Assess and treat for dysphagia pre-discharge

High Protein Oral Nutrition Supplements Essential!

- Caloric Delivery 3000-4000 kcal/day for 6 months – 2 years
- Protein Goals: 1.2-2.0 g/kg/day

Supplements

- Vitamin D – If Deficient – 50,000 I.U. D3 2 x week for 2-4 weeks- then 2000 I.U./day
- HMB- 3g/day
- Consider Probiotics
- Consider Anabolic Agents
  - ▶Propranolol- Adult Starting Dose- 0.2-0.6 mg/kg/d- Titrate to HR < of 20% or < 95 BPM
  - ▶Oxandrolone- Adults: 10 mg BID PO

Role of specific anabolic/anti-catabolic agents, vitamin D and microbiome/probiotics in recovery

Anabolic/Anticatabolic Agents

Data from the large HP-ONS trial using HMB above (Deutz et al. 2016) and other recent review articles (Stanojcic et al. 2016) emphasise that anabolic and anti-catabolic interventions, such as propranolol, oxandrolone and other agents targeted at restoring lean muscle mass (such as HMB) may be vital in optimal recovery and survival post-ICU. As shown in **Table 1**, it is likely targeted nutrition with adequate protein delivery and muscle recovery-targeted agents when combined with exercise will play a vital role in improving survival and recovery of QoL post-ICU (Wischmeyer and San-Millan 2015). The data for these novel anabolic/anti-catabolic agents are covered in detail by a recent review by Stanojcic and colleagues (Stanojcic et al. 2016). These interventions are summarised in **Table 1**.

Vitamin D

A rapidly growing body of data demonstrate a significant portion of the U.S. (and industrialised world) population is Vitamin D deficient (Holick 2007) and data in ICU and surgical patients show that Vitamin D deficiency has a significant relationship to postoperative complications and adverse ICU outcomes (Iglar and Hogan 2015; Higgins et al. 2012; Moromizato et al. 2014). A key recent RCT published in *JAMA* showed ICU patients with Vitamin D levels < 12 ng/ml experienced a significant improvement in hospital survival when vitamin D was aggressively supplemented (Vitamin D_3 or placebo given orally or via nasogastric tube once at a dose of 540,000 IU followed by monthly maintenance doses of 90,000 IU for 5 months) (Amrein et al. 2014). This will be a difficult dose for many centres to administer if concentrated Vitamin D solutions

are not available. Alternatively, a recent double-blinded pilot RCT of 50,000 IU vitamin D_3 or 100,000 IU vitamin D_3 daily for 5 consecutive days enterally was conducted (Han et al. 2016). There was a significant decrease in hospital length of stay over time in the 50,000 IU D_3 / day and 100,000 IU D_3 /day groups compared to the placebo group (25 ± 14 and 18 ± 11 days compared to 36 ± 19 days, respectively; p = 0.03). Thus, vitamin D levels are recommended to be checked at ICU admission and once weekly after in all septic shock patients. A repletion dose of 100,000 units of Vitamin D3 for 5 days in the first week and once-twice weekly thereafter (monitoring levels) for the ICU stay in patients found to be deficient (< 30 ng/ml) is reasonable. Further, the emerging role for Vitamin D to reduce mortality in vitamin D deficient ICU patients has been recently reviewed by Christopher (2016). Correction of Vitamin D deficiency is essential for recovery of muscle mass and for optimising patient outcomes. In the post-ICU discharge setting, Vitamin D supplementation should consist of Vitamin D3 at 50,000 IU 2 x weekly for 2 weeks followed by 2000 IU/day. Larger trials on the role of vitamin D supplementation in sepsis and critical illness are currently underway.

Microbiome/Probiotics

Finally, new data expanding our understanding of the microbiome in the ICU and "dysbiosis" therapies including probiotics and faecal microbiota transplantation have been described by our research group (Wischmeyer et al. 2016; McDonald et al. 2016). Dysbiosis results from many factors, including ubiquitous antibiotic use and overuse. Despite advances in antibiotic therapy, infections and mortality from often multidrug-resistant organisms (i.e. *C. Difficile*) are increasing. This raises the question of whether restoration of a healthy microbiome via probiotics or other "dysbiosis therapies" would be an optimal alternative, and should be a parallel treatment option with antibiotics. This may be particularly true as patients recover following ICU. Our research group's recently published updated meta-analysis of 14 randomised controlled trials (RCT) found that probiotic therapy significantly reduced the incidence of infectious complications in the ICU (RR 0.80, 95% CI 0.68 to 0.95, p = 0.009) (Manzanares et al. 2016). Further, probiotics (Goldenberg et al. 2013) or faecal microbial transplantation (Kassam et al. 2013, Gupta et al. 2016) have been successful as an intervention in *C. Difficile*. Specifically, a meta-analysis looking at probiotic use for the prevention of *C. Difficile*-associated disease (CDAD) combined 23 studies and over 4,200 patients and found probiotics reduced CDAD incidence 64% and mitigated the side effects associated with the use of CDAD-specific therapy (Goldenberg et al. 2013). This contributes to recent recommendations that probiotics should be considered to prevent infection in ICU (criticalcarenutrition.com). It is possible that not only does a patient's LBM and nutrition status need to be recovered, but also recovery of their microbiome may be required to optimise recovery. This may indicate that repletion or "re-sodding" of beneficial bacteria known to be lost following critical illness could begin to provide a targeted therapeutic avenue to pursue following ICU discharge.

Conclusions

In conclusion, we need to consider basic metabolism and historic understanding of starvation and recovery to employ targeted nutritional care to our critically ill patients as they recover following ICU discharge. If we are to optimise patient outcomes and start creating "survivors" we must optimise nutrition delivery post-ICU. It is clear that most patients will be unable to take in adequate nutrition using traditional oral "food"-based diets. It is essential we utilise high protein oral nutrition supplements (HP-ONS) to provide a realistic opportunity for our patients to achieve adequate calorie and protein delivery during the years required to recover functional lean body mass post-ICU discharge. We also must address issues such as dysphagia and need for targeted rehabilitation exercise efforts post-discharge. Finally, we must learn to target and incorporate nutritional therapies such as vitamin D, probiotics, and anabolic/anti-catabolic agents to optimise our patients' chance to survive and thrive against all evolutionary odds. We have long known Mother Nature does not want our ICU patients to win this war and become *"survivors…and not victims"*. But, to begin winning this war on long-term ICU outcomes and give our patients back the lives they came to us to restore, we must ensure, especially post-ICU discharge, our patients get enough nutrition for enough time post-ICU discharge! ■

Conflict of interest

Paul Wischmeyer is an associate editor of *Clinical Nutrition* (Elsevier). He has received grant funding related to this work from the NIH NHLBI R34 HL109369, Canadian Institutes of Health Research, Baxter, Fresenius, Lyric Pharmaceuticals, Isomark Inc and Medtronics. Dr. Wischmeyer has served as a consultant to Nestle, Abbott, Fresenius, Baxter, Medtronics, Nutricia, and Lyric Pharmaceuticals, and Takeda for research related to this work. Dr. Wischmeyer has received honoraria or travel expenses for lectures on improving nutrition care in illness from Abbott, Fresenius and Medtronics.

Abbreviations

CDAD C. Difficile-associated disease
FMT faecal microbiota transplantation
HP-HMB ß-Hydroxy ß-Methylbutyrate
HP-ONS high protein oral nutrition supplements
ICU intensive care unit
ONS oral nutrition supplements
PICS post-intensive care syndrome
RCT randomised controlled trial
REE resting energy expenditure
QoL Quality of life
SGA subjective global assessment
TEE total energy expenditure

References

Amrein K, Schnedl C, Holl A et al. (2014) Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA, 312: 520-30.

Brodsky MB, Huang M, Shanholtz C et al. (2017) Recovery from dysphagia symptoms after oral endotracheal intubation in acute respiratory distress syndrome survivors. A 5-year longitudinal study. Ann Am Thorac Soc, 14: 376-83.

Cawood AL, Elia M, Stratton RJ (2012) Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev, 11: 278-96.

Christopher KB (2016) Vitamin D and critical illness outcomes. Curr Opin Crit Care, 22: 332-8.

Deutz NE, Matheson EM, Matarese LE et al. (2016) Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial. Clin Nutr, 35: 18-26.

Dinglas VD, Aronson Friedman L, Colantuoni E et al. (2017) Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med, 45: 446-53.

Elia M, Normand C, Norman K et al. (2016) A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in the hospital setting. Clin Nutr, 35: 370-80.

Goldenberg JZ, Ma SS, Saxton JD et al. (2013) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev, 5: CD006095.

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

Treatment of bleeding patients during therapy with direct oral anticoagulants

Results from the French registry: GIHP-NACO

Pierre Albaladejo
Professor of Anaesthesiology and Critical Care Medicine
Grenoble-Alpes University Hospital
Grenoble, France

palbaladejo@chu-grenoble.fr

Presents results from a registry detailing information about the management of bleeding patients in the emergency room, operating room or intensive care unit during therapy with direct oral anticoagulants.

Background

There is a large literature on the efficacy of direct oral anticoagulants (DOAC) to prevent stroke or systemic embolic events in patients with atrial fibrillation or to treat venous thromboembolism. DOAC, which include direct anti-Xa and thrombin inhibitors, have a favourable risk-benefit profile. However, as for any anticoagulant, they are associated with spontaneous or provoked haemorrhagic risk. The meta-analysis by Ruff and colleagues of trials comparing patients treated with Vitamin K antagonists (VKA) to patients treated with DOAC showed that with DOAC there were significant reductions in stroke, intracranial haemorrhage and mortality, similar to warfarin, but increased gastrointestinal bleeding.

The challenge remains to manage bleeding, emergency surgery or invasive procedures in patients treated with DOAC. Current French and European guidelines recommend use of haemostatic agents, such as prothrombin complex concentrate (PCC) and antidotes for the treatment of life-threatening bleeding associated with the use of DOAC (Albaladejo et al. 2017a; Kozek-Langenecker et al. 2017).

However, there is a lack of data and we are still trying to develop strategies to manage patients receiving DOAC who are bleeding and who need urgent surgery.

DOAC and coagulation assays

Steiner and colleagues showed that the sensitivity of usual coagulation tests to DOAC is quite variable (Steiner et al. 2013). It depends on the test and the DOAC.

For patient management in anaesthesia and critical care, we need a test that can:

1. Detect significant plasma concentration that could interfere with haemostasis.
2. Eventually attest that a reversal strategy is effective.

The mechanism of action of PCC is different to reverse the anticoagulation effects of VKA or DOAC (**Figure 1**).

In patients anticoagulated with VKA, PCC will replace the factors. In patients anticoagulated with DOAC, PCC acts by overwhelming inhibition of factor IIa or factor Xa, depending on the DOAC involved.

There are several animal studies on direct oral anticoagulants. For example, the study by Pragst and colleagues showed that with 50 IU/kg you reduce bleeding to control animals. Similar studies for apixaban or rivaroxaban have been completed.

In a study that measured thrombin generation times in healthy volunteers receiving a dose of 20 mg rivaroxaban or 150 mg dabigatran, after 2 hours a new measurement was performed for the drug effect of increasing doses of PPSB or FEIBA or rFVIIa. These showed partial or total correction, or even overcorrection (Marlu et al. 2012).

DOAC were first developed without reversal strategies, and antidotes were developed several years after DOAC were approved. Reversal agents include idarucizumab, andexanet alfa (PRT064445) and aripazine (PER977).

Pollack and colleagues (2017) in a prospective cohort study of safety and efficacy of idarucizumab in patients who had serious bleeding or needed an urgent procedure, found that 5g (2 x 2.5g administered within 15 minutes) of idarucizumab reversed the effect of dabigatran.

Lu and colleagues described an antidote for reversal of anticoagulation (Lu et al. 2013). This modified rFXa is produced in Chinese hamster ovary cells. It has no intrinsic procoagulatory effect, but it binds the direct anti-FXa inhibitors.

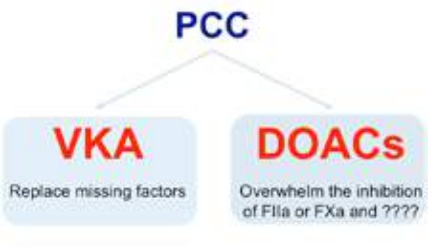


Figure 1.

DOAC direct oral anticoagulant FXa activated factor X PCC prothrombin complex concentrate VKA vitamin K antagonist

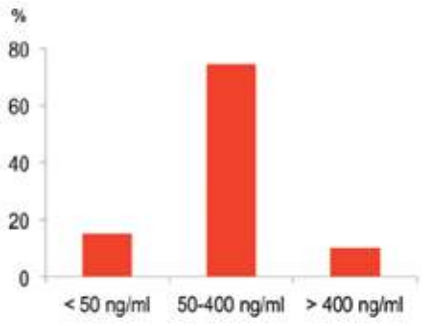


Figure 2.

Plasma concentration of DOAC on admission

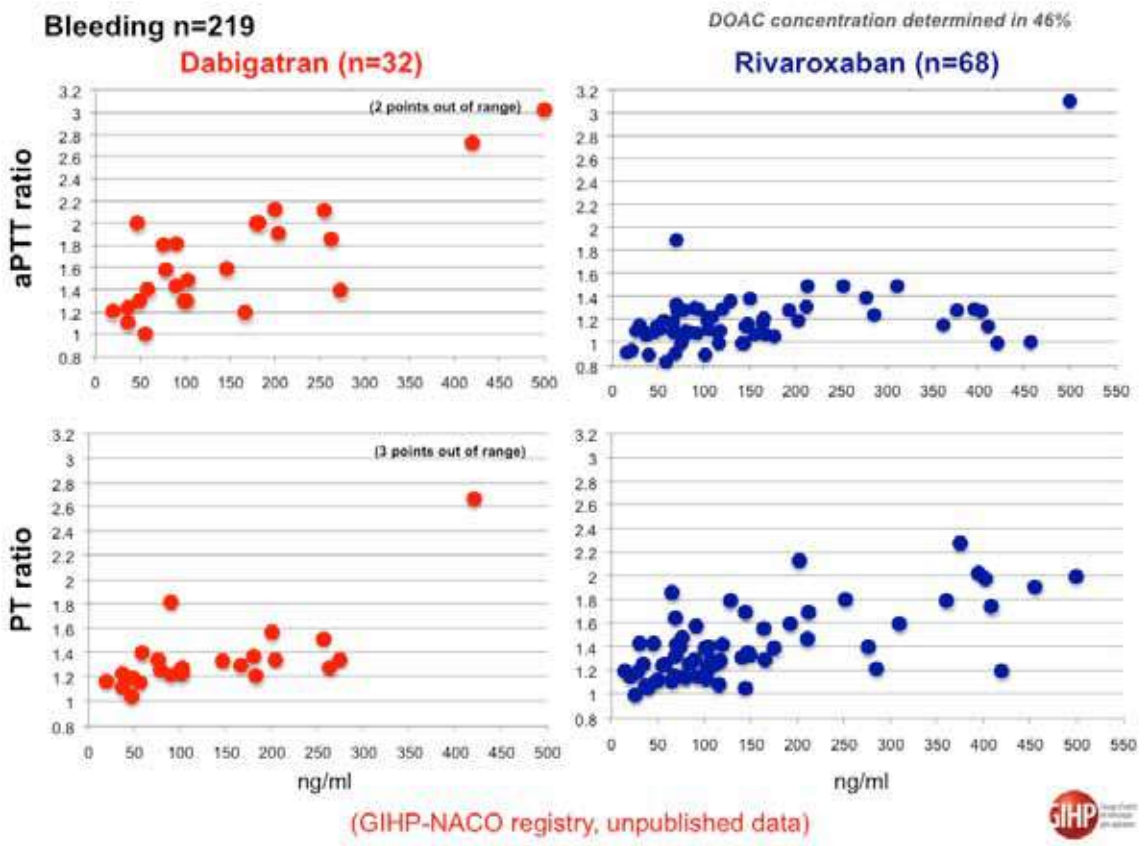


Figure 3 .

aPTT activated partial thromboplastin time DOAC direct oral anticoagulant PTT partial thromboplastin time

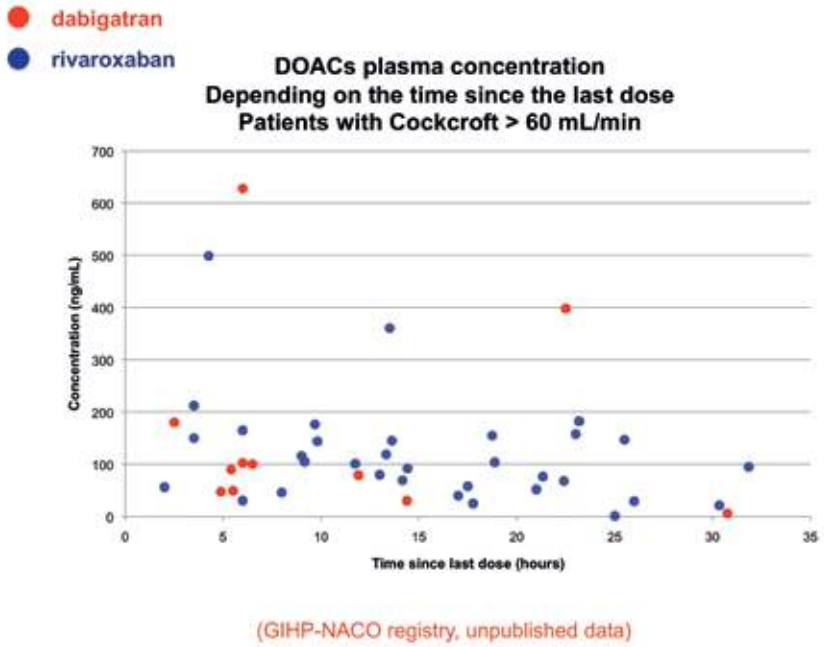


Figure 4.

An investigation of andexanet alfa for acute major bleeding associated with factor Xa inhibitors (Connolly et al. 2016) found that an initial bolus and subsequent 2-hour infusion of andexanet substantially reduced anti-factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors. Effective haemostasis occurred in 79% of the patients.

Connolly's study raises all the problems related to the use of antithrombotic antidotes:

What is the relationship between reversion and a clinical effect? How long is this reversion necessary? Is the antidote prothrombotic? And how to highlight it?

Bleeding in patients treated with DOAC

When we have a patient bleeding while treated by any anticoagulant, we must always consider the use of appropriate supportive and symptomatic treatment:

- Compression
- Surgery
- Embolisation

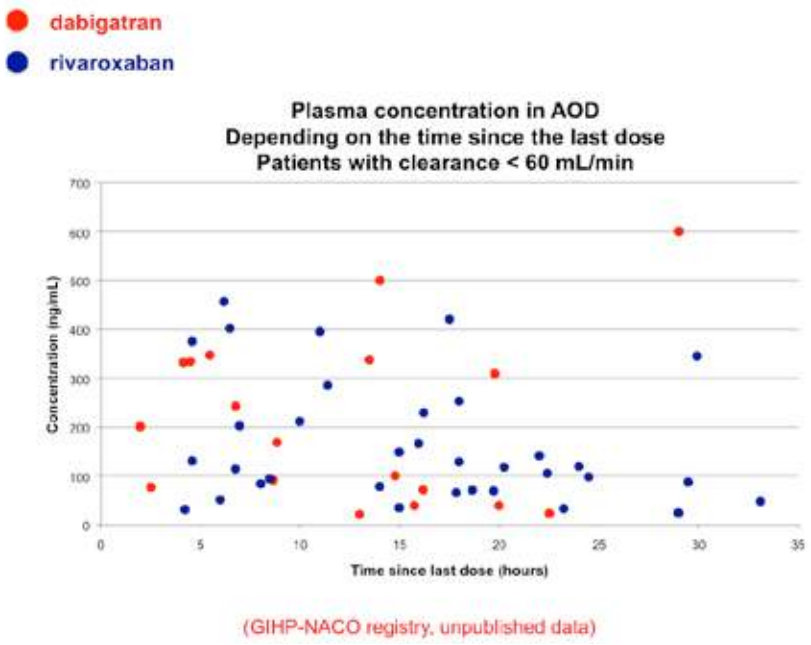


Figure 5.

- Specific procedures
- Fluids
- Transfusion
- Clotting factors
  - Fresh frozen plasma (FFP)
  - Prothrombin complex concentrate (PCC)

Reversal strategies

After all these treatments are used, there are several options to specifically reverse either VKA or DOAC.

Alter the pharmacokinetics of the DOAC by:

a) Time

Waiting is the best antidote. Elimination half-lives are short, unless the patient has a renal dysfunction, particularly with dabigatran.

b) Antidotes

Antidotes exist for dabigatran, and are being developed for anti-Xa agents, and phase III studies are in progress for idarucizumab, for example.

c) Dialysis

This can be considered if the patient is treated with dabigatran, but it is not a simple situation.

d) Charcoal

e) Clotting factors

Administration of clotting factors should be included in local guidelines. In France we have a labelling for VKA, but it is off label to reverse DOAC.

- 4F-PCC First-line
- aPCC First- or second-line

FFP and recombinant activated clotting factor VII (rFVIIa) are not effective, or safe in this indication.

As clinicians, we have to ask: Is it efficient? Is it safe? Is it recommended in guidelines?

GIHP-NACO registry results

The GIHP (French Working Group on Perioperative Haemostasis) established a registry in June 2013 across 41 emergency centres in France and Belgium to collect data on the management of major bleeding in patients receiving DOAC (dabigatran, rivaroxaban or apixaban), who have been hospitalised for major bleeding or emergency surgery (Albaladejo et al. 2017b). The registry prospectively collected data on patient management, focusing on the use of haemostatic agents and the plasma concentration of DOAC. This registry data can be compared with data from large series treated with DOAC antidotes.

Our published results are from 35 centres, between June 2013 and November 2015 (Abaladejo et al. 2017b).

732 patients treated with

–Dabigatran (n=207)

–Rivaroxaban (n=472)

–Apixaban (n=53) and

–Severe bleeding

GI bleeding was present in 37% of patients, intracranial in 24%.

In November 2015 we analysed results from 732 mainly elderly patients, (median age: 78) and most with renal dysfunction.

On admission we took the laboratory results on plasma concentration of DOAC (**Figure 2**) (see p. I). This could be determined in 62% (452/732) of cases.

Figure 3 (see p. II) shows the relationship between activated partial thromboplastin time and prothombin time ratio and concentration of dabigatran and rivaroxaban. These results confirm the uselessness of this lab tests in these situations.

Figure 4 (see p. II) shows DOAC plasma concentration depending on time since last dose.

Figure 5 shows plasma concentration in DOAC depending on the time since the last dose in patients with clearance < 60 mL/ min.

Activated or nonactivated prothrombin complex concentrates were administered in 38% (281/732) of patients.

Table 1.

	All N=732
Transfusion n (%)	261 (35.7%)
Packed red blood cells	243 (33.2%)
Platelets	32 (4.4%)
Fresh frozen plasma	70 (9.6%)
PCC	208 (28.4%)
Total dose IU.Kg-1; median (25th-75th)	42.8 (25.0-50.0)
2nd Dose; n (%)	27 (13.0%)
aPCC	73 (10.0%)
Total dose IU.Kg-1; median (25th-75th)	46.0 (38.1-50.0)
2nd Dose; n (%)	5 (6.8%)
Recombinant Factor VIIa	0
Tranexamic acid (%)	34 (4.7%)
Haemodialysis (%)	9 (1.2%)
Mechanical means*	224 (30.7%)
Intervention for haemostasis control	175 (23.9%)
Endoscopy	97 (55.4%)
Surgery	22 (12.6%)
Embolisation	56 (32.0%)

*compression, gauze packing

aPCC activated prothrombin complex concentrate PCC prothrombin complex concentrate

Reproduced with permission from: Albaladejo P, Samama CM, Sié P et al.; GIHP-NACO Study Group (2017) Management of severe bleeding in patients treated with direct oral anticoagulants: an observational registry analysis. Anesthesiology, 127(1):111-20. https://iii.hm/dir*

Did the bleeding stop after PCC?

Table 2. Did bleeding stop after PCC?

Yes, completely	42.7%
Yes, partially	39.7%
No	17.7%

It is quite difficult with this method and in these heterogeneous patients to assess the efficacy of PCC. In this study adequacy of haemostasis was assessed by local investigators.

By day 30 mortality was 13.5%, variable according to the bleeding site. Patients were also assessed for suspected major cerebral and cardiovascular events (MACCEs) after the bleeding event (**Table 3**).

Table 3.

	All N=732
MACCE; n (%)	56 (7.6%)
Venous thromboembolism	7 (1.0%)
Ischaemic stroke	10 (1.4%)
Systemic emboli	2 (0.3%)
Myocardial infarction	10 (1.4%)
Pulmonary oedema	18 (2.5%)
Cardiogenic shock	12 (1.6%)
All causes of mortality	
n	99
% [CI 95%]	13.5% [11.0-16.2]
Mortality among patients with: % [CI 95%]	
Intracranial haemorrhage (spontaneous)	28.4% [21.1-36.6]
Head trauma	16.7% [10.0-25.3]
Gastrointestinal bleeding	12.0% [7.8-17.3]

CI confidence interval MACCE major cerebral and cardiovascular events

Conclusion

The GIHP-NACO registry study showed that plasma concentration was positively related to use of PCC. In this cohort, the mortality rates of patients with severe bleeding were similar to those observed for large series treated with DOAC antidotes. Plasma concentration could therefore be important to identify patients for whom the use or an antidote or PCC (if antidotes are not available) could be useful. ■

Conflict of Interest

Pierre Albaladejo has received research support from CSL Behring, LFB, Octapharma and Sanofi. He is on the scientific advisory board of Boehringer Ingelheim, Bayer, BMS-Pfizer and Daiichi-Sankyo and is a consultant for Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB and Sanofi. He has received honoraria from Boehringer Ingelheim, Bayer, BMS-Pfizer, Daiichi-Sankyo, LFB, CSL Behring and Sanofi and travel support from CSL Behring, BBraun, Boehringer Ingelheim, Bayer, BMS-Pfizer.

Abbreviations

DOAC direct oral anticoagulant
FEIBA factor eight inhibitor bypass activity
FFP fresh frozen plasma
MACCE major cerebral and cardiovascular events
PCC prothrombin complex concentrate
PPSB prothrombin-proconvertin-Stuart factor-antihemophilic factor B
rFVIIa recombinant factor VIIa
VKA Vitamin K antagonists

Key Points

- Treat major bleeding in patients receiving DOAC with predetermined approach
- Perform laboratory tests to show plasma concentration
- GIHP-NACO study showed positive relationship between plasma concentration and use of PCC
- Take symptomatic and supportive measures—and time to treat patients with major bleeding
- DOAC antidotes are increasingly available
- PCC or aPCC use differs depending on bleeding sites and plasma concentrations of DOAC.

References

Albaladejo P, Bonhomme F, Blais N et al.; French Working Group on Perioperative Hemostasis (GIHP) (2017a) Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: Updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP) - September 2015. Anaesth Crit Care Pain Med, 36(1): 73-6.

Albaladejo P, Samama CM, Sié P et al. (2017b) Management of severe bleeding in patients treated with direct oral anticoagulants: an observational registry analysis. Anesthesiology, 127(1): 111-20.

Connolly SJ, Milling TJ Jr, Eikelboom JW et al. (2016) Andexanet alfa for acute major bleeding associated with factor xa inhibitors. N Engl J Med, 375(12): 1131-41.

Kozek-Langenecker SA, Ahmed AB, Afshari A et al. (2017) Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol, 34(6): 332-95.

Lu G, DeGuzman FR, Hollenbach SJ et al. (2013) A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med, 19(4): 446–51.

Marlu R, Hodaj E, Paris A et al. (2012) Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost, 108(2): 217-24.

Pollack CV Jr, Reilly PA, van Ryn J et al. (2017) Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med, 377(5): 431-41.

Pragst I, Zeitler SH, Doerr B et al. (2012) Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost, 10(9): 1841-8.

Steiner T, Böhm M, Dichgans M et al. (2013) Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. Clin Res Cardiol, 102(6): 399-412.

Fibrinogen concentrate in elective complex cardiac surgery

A monocentric trial

Arno Nierich
Cardiac Anesthesiologist-Intensivist
Isala Clinics
Zwolle, the Netherlands

a.p.nierich@isala.nl

Presents the results from a randomised controlled trial which aimed to determine if fibrinogen concentrate infusion reduces intraoperative blood loss in cardiac surgery patients.

Background

Excessive bleeding is a common complication in cardiac surgery, and may result in the need for red blood cell (RBC) transfusion. Intraoperative bleeding during cardiac surgery is often treated with coagulation factor concentrates (CFCs). As yet, however, their efficacy has not been conclusively determined.

Since 1980 our knowledge of damage from transfusion has increased. Risks include infection, effects on the immune system, transfusion-related acute lung injury and risks due to the age of transfused blood (Isbister et al. 2011). Healthcare systems need to also be aware of the associated costs. As doctors it is our challenge and duty to reduce preventable damage from blood transfusion.

Patient blood management

The evidence-based multidisciplinary approach to optimising care of patients who may need transfusion is known as patient blood management (PBM). We know there is considerable variation in perioperative blood transfusion rate. For example, an analysis of 102,470 patients who underwent coronary artery bypass graft surgery at 792 hospitals in the United States found that rates of blood transfusion ranged from 7.8% to 92.8% for red blood cells (Bennett-Guerrero et al. 2010). PBM can also reduce the need for blood transfusions. In cardiac surgery, a study of Jehovah's Witnesses, who refuse blood products, found no difference in morbidity and mortality if patients are evaluated with a multidisciplinary approach to blood management (Moraca et al. 2011).

At Isala Clinics, we have researched patient blood management, including tailor-made transfusion protocols (Bilecen et al. 2014), and the role of point-of-care testing and fibrinogen concentrate (Bilecen et al. 2013). We implemented a specific transfusion protocol for cardiac surgery, and conducted an intervention study to evaluate its effects on transfusion and clinical events (Bilecen et al. 2014). The protocol included giving component therapy and fibrinogen at the end of the schedule. If we measured fibrinogen less than 1g/L we added 2g of extra fibrinogen. If it was more than 1g/L based on the Clauss measurement, we did not give fibrinogen. The cardiac surgery-specific transfusion protocol resulted in fewer patients transfused with RBCs and fresh frozen plasma (FFP) and a lower incidence of myocardial infarction.

Fibrinogen concentrate therapy

We conducted a cohort study to evaluate the effect of fibrinogen concentrate therapy on postoperative blood loss and transfusion and occurrence of clinical events in complex cardiac surgery; 264/1075 patients received fibrinogen concentrate during surgery (Bilecen et al. 2013). There was no reduction in postoperative blood loss and transfusion (intensive care unit [ICU] blood loss: OR 1.02 (0.91-1.14) and ICU transfusion: OR 1.14 (0.83-1.56) and no increase in risk for adverse clinical events. However, the haemostatic effect may have been attenuated by the low doses and relatively late administration of fibrinogen concentrate therapy.

Randomised controlled trial

Therefore we initiated a prospective single-centre, randomised, placebo-controlled, double-blind clinical trial to find out if fibrinogen concentrate infusion dosed to achieve a post-infusion plasma fibrinogen level of at least 2.5 g/L in high-risk elective cardiac surgery patients 18 years or over with intraoperative bleeding reduced intraoperative blood loss (Bilecen et al. 2017).

The primary outcome of the study was intraoperative blood loss measured between intervention and closure of the chest when surgery ended. Secondary outcomes included the measured blood loss at 1, 3, 6,12 and 24 hours after the intervention; the proportion of patients who received transfusion; and number of

Figure 1.

IMP investigational medicinal product

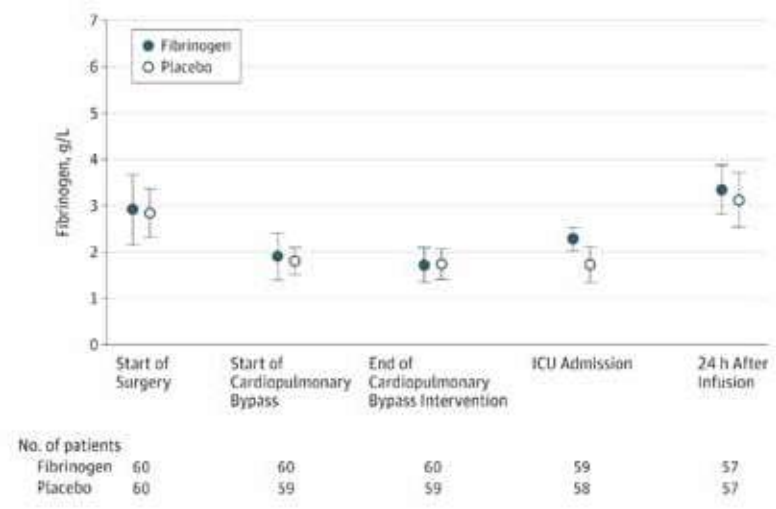


Figure 2. Fibrinogen concentrate dosing

Table 1. Primary, secondary and exploratory study outcomes

	Median (IQR), mL			
	Fibrinogen (n = 58)	Control (n = 57)	Absolute Difference (95% CI)	P Value
Primary Outcome				
Blood loss between intervention and chest closure	50 (29-100)	70 (33-145)	20 (−13 to 35)[a]	.19
Secondary or Exploratory Outcome				
No. of patients	58	59		
Blood loss in the ICU/time interval starting from admission				
0-1 h	70 (35-130)	90 (46-149)		
>1-3 h	80 (50-156)	110 (40-220)		
>3-6 h	100 (54-169)	110 (60-208)		
>6-12 h	110 (80-160)	125 (83-224)		
>12-24 h	130 (80-180)	160 (90-270)		
Cumulative 24-h blood loss	570 (390-730)	690 (400-1090)	120 (−45 to 355)[a]	.047[b]

ICU, intensive care unit IQR, interquartile range. Time point "intervention" is defined as moment of infusion of study medication.
a 95%confidence interval of difference in medians is based on a nonparametric bootstrap procedure (10 000 bootstraps with replacement).
b P value is based on the constructed mixed-model for repeated measurements.

Table 2. Secondary transfusion outcomes

	Fibrinogen (n = 58)	Control (n = 59)
Patients who received transfusion between intervention and chest closure, No. (%)		
Red blood cells	0	3 (5)
Fresh-frozen plasma	0	1 (2)
Platelets	2 (3)	2 (3)
Any transfusion	2 (3)	4 (7)
Patients transfused between intervention and 24 h, thereafter, No. (%)		
Red blood cells	10 (17)	20 (33)
Fresh-frozen plasma	9 (15)	13 (22)
Platelets	9 (15)	13 (22)
Any transfusion	20 (33)	23 (38)
Transfusion units between intervention and 24 h thereafter, median (IQR)		
Red blood cell transfusion units	0 (0-1)	0 (0-4)
Fresh-frozen plasma transfusion units	0 (0-2)	0 (0-4)
Platelets transfusion units	0 (0-1)	0 (0-1)
Any transfusion units	0 (0-2)	0 (0-8)

units of RBCs, FFP or platelet concentrate.

The aim was to achieve surgical haemostasis after heparin reversal. It was the surgeons' decision when to start the 5-minute bleeding time. Once patients had bled for 5 minutes they were entered into the treatment algorithm if they were bleeding >60 mL and <250 mL. The intervention was considered to have started on initiation of infusion of the study medication (**Figure 1**) (see p. V).

Over the four years of the trial, over 700 patients had complex cardiac surgery, of which 40% were eligible for the trial. Of the eligible patients, 43% did not agree to participate; 203 patients agreed to participate, of which 73 (36%) experienced no intraoperative bleeding and 10 were excluded for other reasons. We suggest that the high number of patients that experienced no intraoperative bleeding may be due to the Hawthorne effect—performing differently when being observed. This group of patients had very extensive surgical haemostasis before we started with the 5 minutes bleeding time, much longer than usual. The surgeons may have perceived that they were a better surgeon if they were not included in the trial, and also that after closure of the chest the microvascular bleeding was now the problem for the anaesthesiologist.

The patients were randomised to receive either the placebo or the intervention drug in doses between 60ml and 250ml. The fibrinogen doses were calculated based on plasma fibrinogen levels at the end of cardiopulmonary bypass measured using the Clauss method (**Figure 2**).

Results

Primary outcome

Among patients with intraoperative bleeding who received infusion of fibrinogen concentrate, compared with placebo, there was no significant difference in blood loss measured from the time of the fibrinogen infusion and chest closure (p = 0.19) (**Table 1**).

fibrinogen group
(median, 50 mL; IQR, 29-100 mL)
control group
(median, 70 mL; IQR, 33-145 mL)
absolute difference:
20 mL (95% CI, −13 to 35 mL)

Cumulative 24-hour blood loss was lower in the fibrinogen group compared with placebo (p = 0.047).

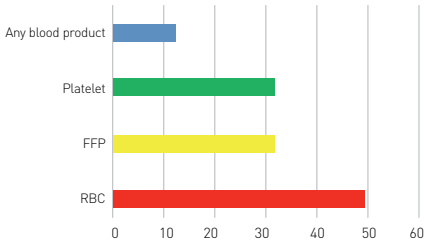


Figure 3. % reduction of transfusion

FFP fresh frozen plasma RBC red blood cells

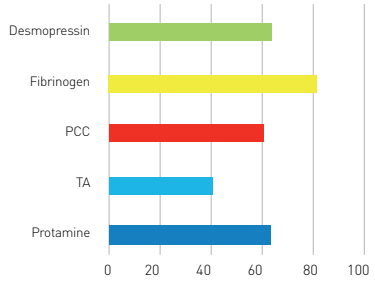


Figure 4. % reduction in procoagulants

PCC prothrombin complex concentrate TA tranexamic acid

Table 3. Procoagulants and antifibrinolytics use during surgery and ICU

	Fibrinogen (n = 60)	Control (n = 60)
During surgery, patients receiving, No. (%):		
Tranexamic acid	59 (98%)	60 (100%)
Desmopressin	42 (70%)	41 (68%)
Prothrombin complex concentrate	5 (8%)	2 (3%)
Recombinant factor VIIa	0 (0%)	0 (0%)
During ICU period, patients receiving, No. (%):		
Protamine	3 (5%)	8 (13%)
Tranexamic acid	9 (15%)	15 (25%)
Desmopressin	3 (5%)	8 (13%)
Prothrombin complex concentrate	4 (7%)	10 (17%)
Fibrinogen concentrate	1 (2%)	6 (10%)
Recombinant factor VIIa	0 (0%)	0 (0%)

Table 4. Clinical adverse events within 30 days

	No. of Events[a]	
	Fibrinogen (n = 60)	Control (n = 60)
In-hospital mortality	2	0
Stroke	4	1
Transient ischaemic attack	0	1
Myocardial infarction	3	1
Renal insufficiency or failure	3	2
Thromboembolism	0	0
Allergic reaction	0	0
Infections	3	2
Rethoracotomy (≤5 d)	4	5

The duration of primary outcome collection was 4.2 minutes (95% CI, 0.4-8.0 minutes) in the fibrinogen group and 8.7 minutes (95% CI, 5.2-12.1 minutes) in the control group.

However, other than these times do suggest these were not the best and fastest surgeons ever. This is why the primary endpoint was different than we expected. We expected that the moment there is a bleeding patient everyone would wait for closure and this would lead to a difference in blood loss in the patient and of course a difference in the intraoperative time factor.

Secondary outcomes

There were fewer patients in the fibrinogen group and fewer units of blood units used (**Table 2**). However, the study was not adequately powered to test the secondary outcomes. The percentage of reduction in transfusion is shown in **Figure 3**.

After surgery, a single patient (2%) in the fibrinogen group and 6 patients (10%) in the control group received additional fibrinogen concentrate. This confounds the effect on overall outcomes.

Procoagulants and antifibrinolytics use is shown in **Table 3**. The percentage of reduction is shown in **Figure 4**.

Clinical adverse events within 30 days

There were more adverse events in the fibrinogen group (**Table 4**). Two patients died, and 4 suffered a stroke. One patient in the control group suffered a stroke, and one a transient ischaemic attack. The trial was not designed to evaluate major adverse cardiac events and there was no screening for embolic risk aortic disease.

Almost 50% (9/19) of adverse events occurred in two patients **(Table 5)** (see p. VIII). Also one stroke occurred in a placebo patient with a fibrinogen level of 0.6g/l.

Transfusion protocol for cardiac surgery

At Isala Clinics we now use the following transfusion protocol **(Figure 5)** (see p. VIII). We conduct viscoelastic tests (ROTEM) to guide haemostatic therapies. Maegele and colleagues have provided a useful haemotherapy algorithm (Maegele et al. 2017).

Conclusion

Fibrinogen is effective after complex cardiac surgery in the bleeding patient. Based on the current trial data, fibrinogen is recommended as a first-line therapy with target plasma level 2.5g/L at the moment there is an idea of microvascular bleeding in these patients. Both visco-elostometry as the conventional Clauss method can be used to determine the level of fibrinogen at the end of bypass surgery and to optimise further treatment.

We have the tools and knowledge now to change transfusion management. But changing transfusion management, as with any change, is a major behavioural process. You need to do this together with your own multidisciplinary group, using a change strategy such as the Kotter model (https://www.kotterinternational.com/8-steps-process-for-leading-change). ■

Conflict of Interest

Arno Nierich is the principal investigator for the fibrinogen concentrate trial at Isala Clinics. CSL Behring sponsored the study and donated the bottles of study medication.

Table 5. Data on clinical adverse events, with allocated treatment, infused dose, fibrinogen plasma concentrations and time of event in days after surgery

Participant	Medication	Pre-infusion [fibrinogen g/L][a]	Infusion dose (g)[b]	Post-infusion [fibrinogen g/L][c]	Clinical adverse events						
					Mortality	Stroke	TIA	MI	RI	Infections	Rethoractomy
H-012	fibrinogen	1.6	3	2.4	day +10	day +1		day +1	day +2		day 0
H-161	fibrinogen	0.8	6	1.7	day +5	day +1			day +2		day 0
H-047	placebo	0.5	7	0.6		day 0					
H-140	fibrinogen	1.6	4	2.3		day +1				day +30	
H-155	fibrinogen	2.4	0	2.3		day +6					

MI myocardial infarction RI renal insufficiency or failure TIA transient ischemic attack,
a Plasma fibrinogen concentration at end-CPB.
b Infusion of study medication after removal of cardiopulmonary bypass. For placebo matched number of syringes is infused.
c Plasma fibrinogen concentration at ICU admission.

Key Points

- Implement transfusion management with change strategy
- Multidisciplinary group essential
- Point-of-care and lab monitoring:
  - Part of overcoming the 'blind spot' of coagulation management in operating room and intensive care unit
  - Additional tool in fine-tuning bleeding management
  - Measure fibrinogen level by Clauss as first potential bleeding indication
- Fibrinogen is effective after complex cardiac surgery in the bleeding patient: from rescue medication to first-line therapy with target level 2.5 g/L in the bleeding patient

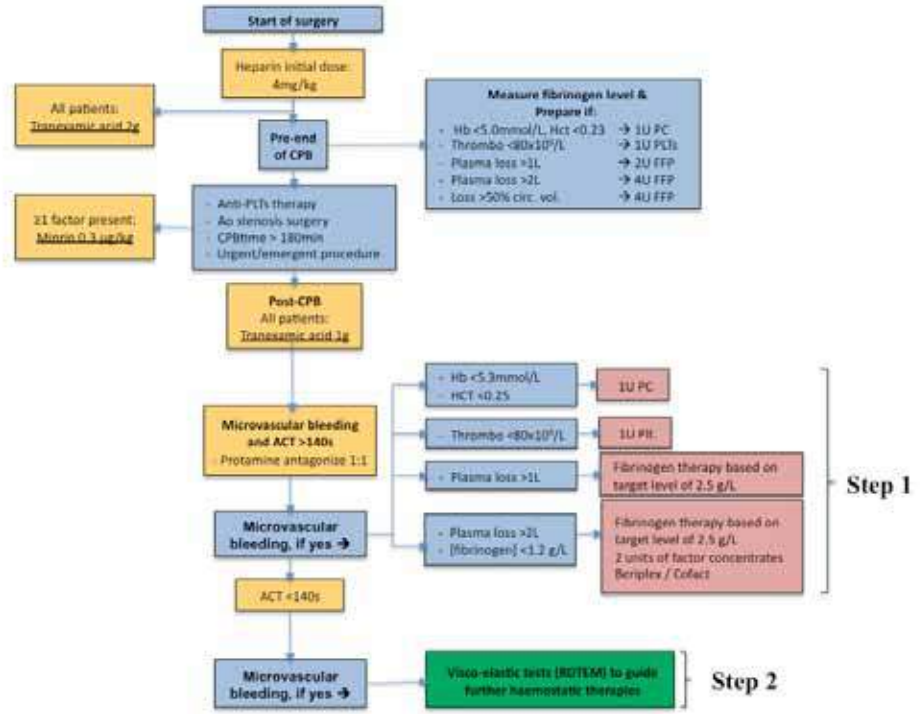


Figure 5. Transfusion protocol for cardiac surgery

References

Bennett-Guerrero E, Zhao Y, O'Brien SM et al. (2010) Variation in use of blood transfusion in coronary artery bypass graft surgery. JAMA, 304(14): 1568-75.

Bilecen S, Peelen LM, Kalkman CJ et al. (2013) Fibrinogen concentrate therapy in complex cardiac surgery. J Cardiothorac Vasc Anesth, 27(1): 12-7.

Bilecen S, de Groot JA, Kalkman CJ et al. (2014) Effectiveness of a cardiac surgery-specific transfusion protocol. Transfusion, 54(3): 708-16.

Bilecen S, de Groot JA, Kalkman CJ et al. (2017) Effect of fibrinogen concentrate on intraoperative blood loss among patients with intraoperative bleeding during high-risk cardiac surgery: a randomized clinical trial. JAMA, 317(7): 738-47.

Isbister JP, Shander A, Spahn DR et al. (2011) Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev, 25(2):89-101.

Moraca RJ, Wanamaker KM, Bailey SH et al. (2011) Strategies and outcomes of cardiac surgery in Jehovah's Witnesses. J Card Surg, 26(2): 135-43.

Abbreviations

CFC coagulation factor concentrates
FFP fresh frozen plasma
ICU intensive care unit
PBM patient blood management
RBC red blood cells

Treatment of trauma-induced coagulopathy with factor concentrates versus treatment with fresh frozen plasma

RETIC study

Petra Innerhofer
Department of Anaesthesia and Critical Care Medicine
Medical University Innsbruck, Austria

petra.innerhofer@tirol-kliniken.at

Presents results of the RETIC study that compared treatment of trauma-induced coagulopathy using coagulation factor concentrates or fresh frozen plasma.

Background

Trauma-induced coagulopathy (TIC) represents a clinical picture resulting from severity of injury, hypoperfusion, blood loss, consumption, dilution and platelet dysfunction. Activation of the protein C system seems to mediate increased fibrinolytic attack. Despite the complex pathophysiology, the clinical picture is quite uniform: low fibrin formation and consequently low clot firmness occur predominantly and are the outcome-related pathologies. In addition, plasmatic test results are more or less impaired, albeit thrombin generation is maintained in the early phase of trauma, and hyperfibrinolysis can be expected in the very severely injured patient.

During the past 10 years coagulation management has gained great importance. Several studies have shown that early and aggressive fresh frozen plasma (FFP) is better than late plasma administration in terms of survival. In addition the evidence that use of coagulation factor concentrates (CF) is an effective alternative has grown. However, only a few study data are available for use of CF and thus both treatments are still recommended by guidelines. The European guideline's recommendation for initial coagulation resuscitation is for either fresh frozen plasma: red blood cell (FFP:RBC) at least 1:2 (evidence grade 1B) or fibrinogen concentrate and RBC (1C) (Rossaint et al. 2016).

RETIC trial

The *Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC)* study focused on treatment of coagulation in major trauma. It was a single-centre, parallel-group, open-label, randomised trial that aimed to compare the efficacy of FFP or CF in reversing TIC, as well as the arising transfusion requirements and development of multiple organ failure (MOF).

The study was terminated early due to institutional review board-mandated, predefined stopping rules; in the plasma arm there was an undesirable harmful effect of massive transfusion. The study received no outside funding. The results are published in *Lancet Haematology* (Innerhofer et al. 2017).

The hypothesis of the study was that the use of CF is superior to FFP for correction of TIC and that this should reduce bleeding and transfusion requirements, and consequently MOF.

The overall primary clinical endpoint was difference in MOF (calculated sample size n=200). The interim analysis was preplanned after 100 included patients.

The main secondary endpoints of the study were:

- transfusion requirements, massive transfusion
- frequency of treatment failure (rescue rate)
- laboratory parameters
- time until reversal of coagulopathy
- other clinical outcome parameters
- post hoc subgroup analysis, analysis adjusted for stratification factors (Injury Severity Score [ISS])

The inclusion criteria for the study were male and female patients ≥ 18–≤ 80 years who had experienced major trauma (ISS >15), who had clinical signs of ongoing bleeding, or who were at risk for significant haemorrhage assessed and judged by the emergency department (ED) team in charge of the patient, and who had the presence of coagulopathy defined by rotational thromboelastometry (ROTEM) —FibTEM assay (10-min value of fibrinogen polymerisation [FibA10] <9 mm) and/or prolonged initia-

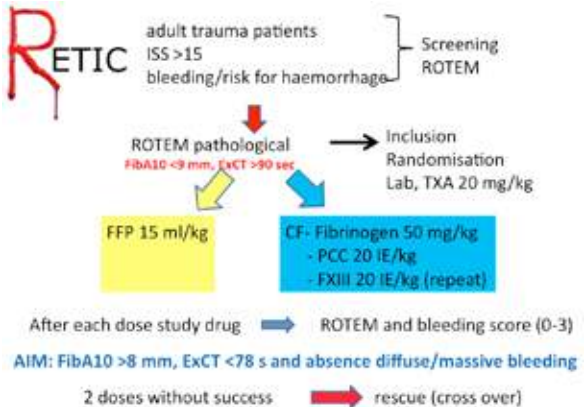


Figure 1.

ExCT Coagulation time of extrinsically activated rotational thromboelastometry assay FibA10 fibrin polymerisation at 10 min FXIII coagulation factor XIII concentrate ISS Injury Severity Score PCC prothrombin complex concentrate ROTEM rotational thromboelastometry TXA tranexamic acid

Table 1. Study population

	CF (n=50)	FFP (n=44)
Age (ys)	43 (27-51)	43 (24-56)
Male sex (n)	38 (76%)	32 (73%)
ISS (pt)	35 (29-42)	30 (24-45)
Brain injury (n)	25 (50%)	21 (48%)
Time to ED (min)	62 (40-90)	57 (44-85)
Systol. BP <90 mmHg (n)	19 (38%)	10 (23%)
Crystalloids (ml)	500 (250-1000)	500 (500-1000)
Colloids (ml)	400 (0-500)	250 (0-500)
BE (mmol/l)	–4.4 (–6 to –2)	–4.2 (–7.8 to –3)
Lactate (mmol/l)	2.2 (1.6-3.2)	2.3 (1.6-3)
Hyperfibrinolysis (n)	4 (8%)	2 (4.5%)
Immediate surgery	44 (88%)	36 (81.8%)

BE base excess BP blood pressure CF coagulation factor concentrate FFP fresh frozen plasma ISS Injury Severity Score

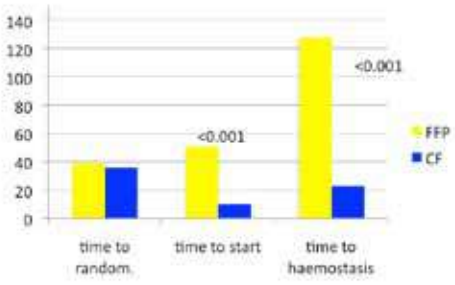


Figure 2. Time intervals

CF coagulation factor concentrate FFP fresh frozen plasma

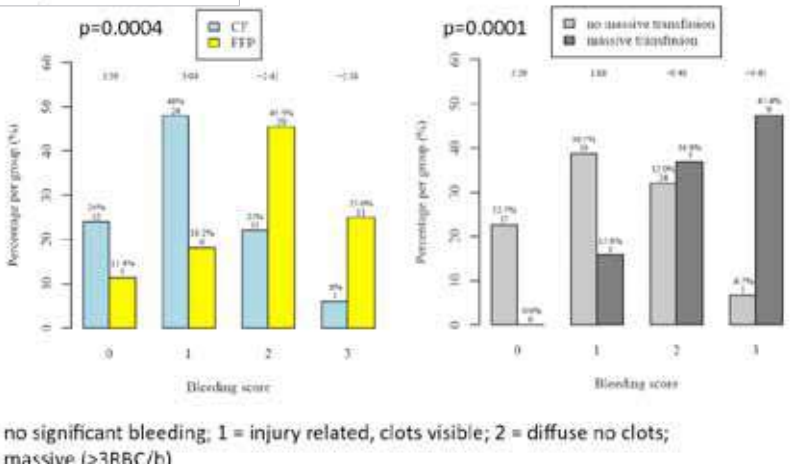
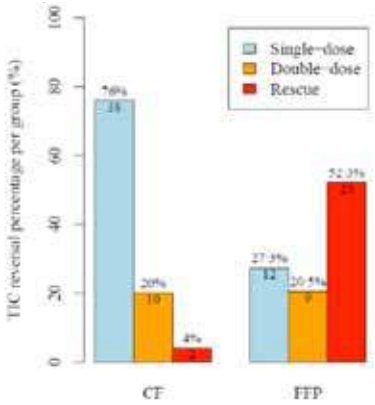


Figure 3. Bleeding score after first dose, CF n=50, FFP n=44, CF coagulation factor concentrate FFP fresh frozen plasma



Rescue rate after double-dose
FFP vs CF: **52.3% vs 4%** p<0.001
OR 25.34 (CI 5.47–240.03) **NNT (CF) = 2.07**

Figure 4. Treatment efficacy

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma NNT number need to treat OR odds ratio

tion of coagulation in the extrinsically activated ROTEM (ExTEM) assay (coagulation time of ExTEM assay [ExCT] >90 s).

Patients were excluded from the study if they had sustained a lethal injury, received cardiopulmonary resuscitation at the scene, had an isolated brain injury, burn injury, avalanche injury, had received FFP or coagulation factor concentrates before ED admission, were admitted to ED more than 6 hours after the trauma, or had known use of oral anticoagulants, or platelet aggregation inhibitors within 5 days before injury or a known history of severe allergic reaction to plasma products.

Adult trauma patients with severe injury were screened by one of the study team and a ROTEM was performed (**Figure 1**) (see p. IX). If ROTEM was pathological the patient was included. Using closed envelopes the patient was allocated to one of the two groups, a blood sample for detailed coagulation analysis was drawn and all patients received a tranexamic acid bolus. Patients in the plasma group received FFP at a single dose of 15ml/kg, the dose recommended by the European guidelines published in 2010 (the protocol was created in 2011) (Rossaint et al. 2010). As plasma is not a single substance but contains factors for thrombin formation, fibrinogen and also FXIII, we needed to consider this in the CF arm to avoid bias. Patients in the CF group received fibrinogen 50 mg/kg, if indicated also prothrombin complex concentrate (PCC) 20 IE/kg and FXIII 20 IE/kg was administered in patients needing double-dose fibrinogen (repeat).

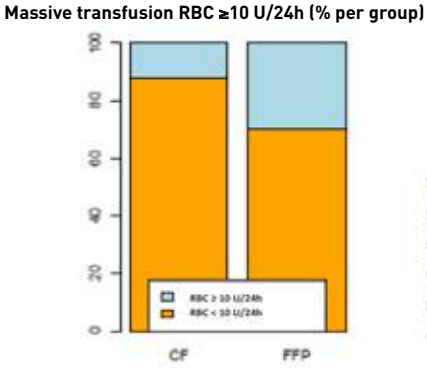
After study drug administration, ROTEM was checked again and the bleeding situation was assessed. Successful therapy was defined as normalised ROTEM and absence of diffuse or massive bleeding. Patients who showed insufficient reversal of TIC received a second dose of the study drug, and if this did not work rescue therapy was started, meaning patients of the CF group received plasma, patients of the plasma group received CF. Each treatment loop consisted of a maximum 4 steps—two times study drugs according to randomisation and one or two times rescue therapy.

Table 1 shows the baseline characteristics of the study population.

The time to start of therapy was significantly different between groups (**Figure 2**). The time to start was longer in the plasma group. This is a clear advantage of using CF as they are immediately available and liquid plasma is not licensed in Austria. The time to haemostatis and normalised ROTEM was significantly longer in the plasma group at about 2 hours. Taking into account the longer time to start of therapy of FFP the difference is still about 1 hour. **Figure 3** shows the bleeding score after first dose.

Patients in the plasma group had more frequently diffuse and massive bleeding after the first study drug administration than patients of the CF group. The bleeding score after first study drug administration was significantly associated with need of massive transfusion.

Figure 4 shows the percentage of patients who showed reversal of TIC after a single dose, double dose or need for rescue therapy after having received a double dose of study drugs. There was not only a big difference in success after single dose, but most importantly more than 50% of patients in the plasma group needed



CF vs FFP : MT 12% vs 29.5%
p=0.042; **OR 3.038** (CI 0.0951–10.873)
Log. Regression/ISS/TBI
p=0.0169; **OR 4.2421** (CI1.3630–5.0935)
NNH (FFP) = 5.7

Figure 5. RBC

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma ISS Injury Severity Score MT massive transfusion NNH number needed to harm OR odds ratio RBC red blood cells TBI traumatic brain injury

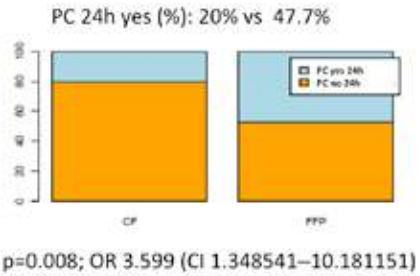


Figure 6. Platelets

CI confidence interval OR odds ratio PC platelet concentrate

Table 2. Study drugs

	CF (n=50)	FFP (n=44)	p-value
FFP n U	 2 5 (5-5)	 44 14 (10-14)	 N/A N/A
FC n g	 50 (100%) 8 (5-10)	 23 (52.3%) 5 (4.5-8)	 N/A N/A
PCC n IU	 8 (16%) 2000 (1875-3000)	 2 (4.5%) 850 (675-1025)	 0.09 0.046
FXIII (n)	27 (54%)	11 (25%)	0.006

CF coagulation factor concentrate FC fibrinogen concentrate FFP fresh frozen plasma FXIII coagulation factor XIII concentrate PCC prothrombin complex concentrate

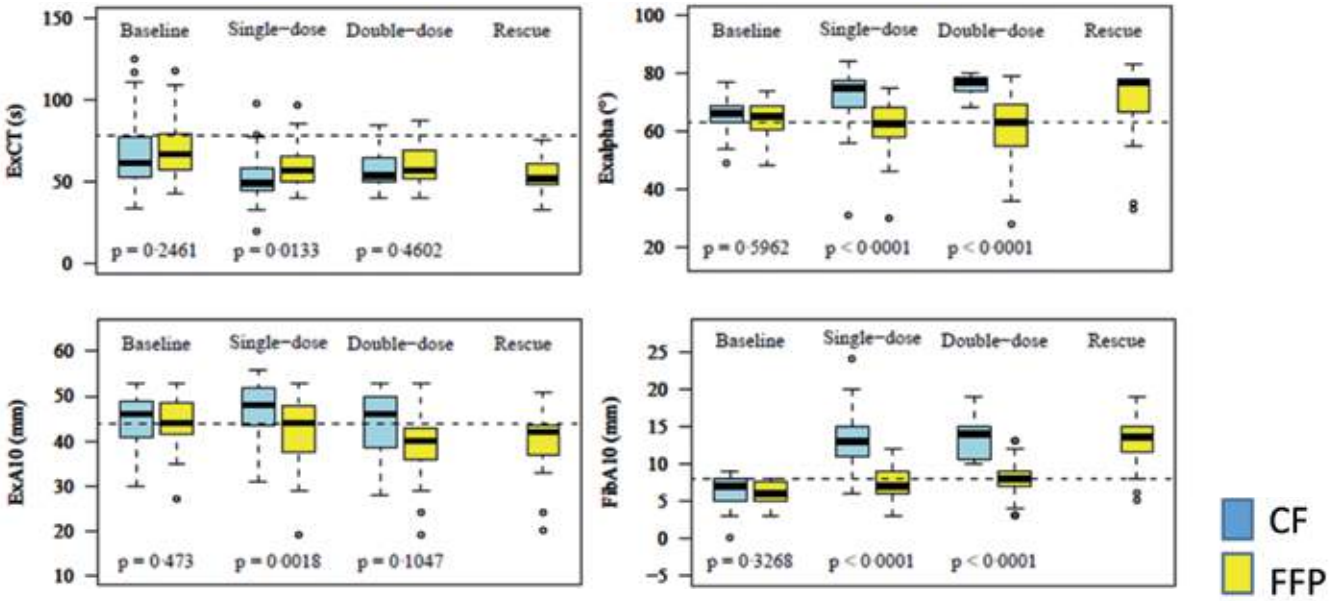


Figure 7. ROTEM parameters

CF coagulation factor concentrate FFP fresh frozen plasma

additional rescue therapy. The odds for receiving rescue were significantly higher for FFP patients and the calculated number needed to treat (NNT) was remarkably low for CF. On average 100 out of 207 patients receiving initial CF treatment will show reversal of TIC, which would have not occurred with initial FFP treatment. **Figure 5** shows RBC transfusion.

The odds for receiving massive transfusion were three-fold higher with plasma. If ISS and brain injury were considered as influencing factors, the odds were four-fold higher with plasma therapy. The calculated NNT was 5.7, meaning that on average 10 out of 57 patients treated initially with FFP need massive transfusion (MT), which would not have occurred with initial CF treatment. We also found a significant difference in numbers of RBC used during the first 24h.

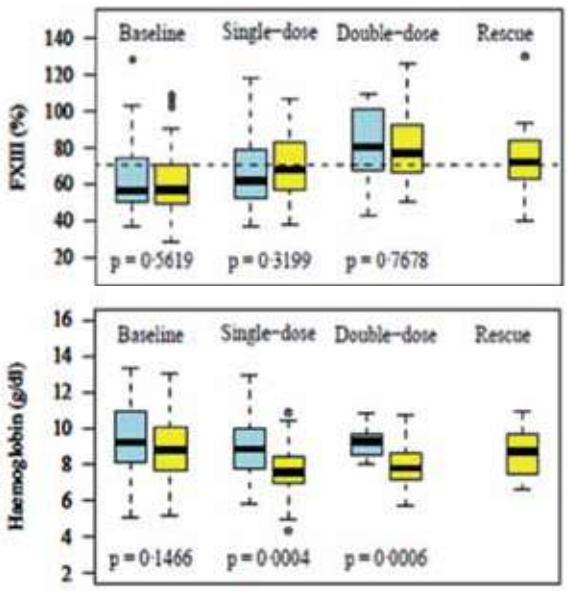
Patients of the plasma group more frequently needed transfusion of platelet concentrates (PC) (**Figure 6**).

Table 2 summarises the dosages of study drugs used in the first 24 hours; important is the finding that patients in the plasma group needed FC after double dose FFP in comparable amounts as did patients receiving FC first-line, meaning nothing had been saved with late fibrinogen concentrate administration. PCC was seldom needed in the CF group; FXIIIc was frequently administered and also needed in the plasma group.

Figure 7 shows the response of ROTEM parameters according to therapy, blue is CF, yellow is plasma. EXCT shortened in both groups, shortest values were reached with CF; Exalpha, EXA10 and FibA10 increased with CF, but remained unchanged or even decreased with plasma.

Baseline CF 50, FFP 44
Single dose CF 50, FFP 44
Double dose CF 12, FFP 32
Rescue FFP 20 (3 patients received rescue at later treatment loops)

Figure 8 (see p. XII) shows levels of FXIII, Hb and platelet count during the first treatment loop.



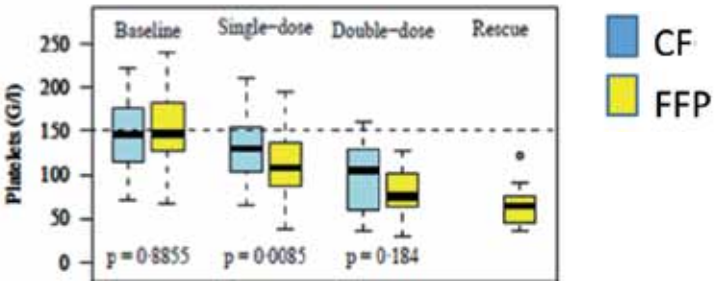


Figure 8. Levels of FXIII, Hb and platelet count during the first treatment loop

CF coagulation factor concentrate FFP fresh frozen plasma Hb haemoglobin FXIII coagulation factor XIII concentrate

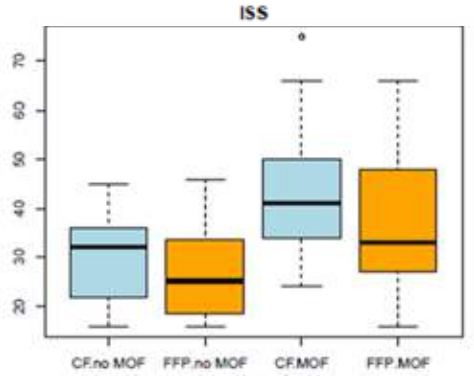


Figure 9. Logistic regression adjusted for stratification factors ISS/TBI: significantly increased risk for MOF with FFP

p = 0.0250, OR 3.1264 (CI 1.1906–8.8756)

CF coagulation factor concentrate FFP fresh frozen plasma ISS Injury Severity Score MOF multi-organ failure TBI traumatic brain injury

FXIII levels were comparable in both groups and at the intended value of 60%. Numbers of platelets and Hb decreased in both groups, lowest values were seen with plasma although these patients received more RBC and PC.

The overall primary clinical endpoint MOF was narrow and not significant with the available limited sample size (the calculated sample size for assessment of MOF was 200 patients) (**Table 3**).

	CF (n=50)	FFP (n=44)	p-value
MOF	25 (50%)	29 (65.9%)	0.1457

Table 3. Multi-organ failure (MOF)

CF coagulation factor concentrate FFP fresh frozen plasma

However, if the influencing factors ISS and brain injury were considered, which were also used for stratification at randomisation, there was an increased risk for MOF with plasma therapy. Patients in the plasma group developed MOF at significantly lower ISS than patients of the CF group (**Figure 9**).

Subgroups	CF only n=48	FFP rescue n=23	FFP only n=21	p-value
MOF	48%	78.3%	52 %	0.0479
		OR 3.839 (CI 1.1323–15.4448), p=0.0209		

Table 4

CF coagulation factor concentrate CI confidence interval FFP fresh frozen plasma OR odds ratio

Finally we also looked at the MOF rate in the 3 subgroups and found a lower risk of MOF in patients receiving first-line CF as compared to those patients receiving first-line plasma and late rescue CF. No difference occurred between the two plasma groups.

Conclusion

Targeted administration of coagulation factor concentrates is more effective than the usual transfusion of fresh plasma in patients with trauma-induced coagulopathy.

First-line administration of CF results in early stop of bleeding, reduced transfusion of all blood components, decreased rate of massive transfusion and decreased risk for MOF. In-hospital mortality was remarkably low with 7.4% and similar in both groups, as was the incidence of thromboembolic events. Thus our treatment concept seems to be quite safe. If you look at the mortality of recent studies including patients with comparable or even lower ISS you see mortality rates of 20 to 35% when transfusion packages are used which contain cryo very late or not at all. Interestingly authors of the last review on the usefulness of fibrinogen concentrate already suggested a probable survival benefit with use of FC (Fominskiy et al. 2016). ■

Conflict of interest

The RETIC study received no funding. Petra Innerhofer has received personal fees from Baxter, Bayer, CSL Behring, Fresenius and LFB, and non-financial support from Tem International outside the study.

Key Points

- Early and effective fibrinogen supplementation important
- Targeted CF-based therapy superior to FFP
- Correction of TIC in 96% with CF, less than 50% with FFP
- Remarkably low NNT with CF (mainly fibrinogen concentrate)
- First-line FFP
  - persisting hypofibrinogenaemia
  - low clot firmness
  - prolonged coagulopathic bleeding
  - increased transfusion of RBC and PC/24 hours
  - increased rate of massive transfusion
  - increased risk of MOF
  - results with continued FFP and without rescue?
- In-hospital mortality rather low with 7.4%

Abbreviations

CF coagulation factor concentrate
ED emergency department
FC fibrinogen concentrate
FFP fresh frozen plasma
FXIII coagulation factor XIII concentrate
Hb Haemoglobin
ISS injury severity score
MOF multiple organ failure
MT massive transfusion
NNT number needed to treat
PC platelet concentrate
PCC prothrombin complex concentrate
RBC red blood cells
ROTEM rotational thromboelastometry
TIC trauma-induced coagulopathy

References

Fominskiy E, Nepomniashchikh VA, Lomivorotov VV et al. (2016) Efficacy and safety of fibrinogen concentrate in surgical patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth, 30(5): 1196-204.

Innerhofer P, Fries D, Mittermayr M et al. (2017) Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol, 4(6): e258-e271.

Rossaint R, Bouillon B, Cerny V et al. (2010) Management of bleeding following major trauma: an updated European guideline. Crit Care, 14(2): R52.

Rossaint R, Bouillon B, Cerny V et al. (2016) The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care, 20: 100.

09 - 10 NOVEMBER
TEL AVIV, ISRAEL

ESA Focus Meeting

REGIONAL ANAESTHESIA IN THE PERIOPERATIVE SETTING 2017

ESA
esahq.org

Euroanaesthesia

THE EUROPEAN ANAESTHESIOLOGY CONGRESS 2018

02 - 04 JUNE
DENMARK, COPENHAGEN

Current challenges in paediatric sedation

Report of the Primex Pharmaceuticals Symposium Euroanaesthesia 2017, Geneva, Switzerland, 4 June 2017

Karin Becke
Head of Department
Department of Anaesthesiology, Paediatric Anaesthesiology and Intensive Care Medicine
Cnopf Childrens Hospital
Hospital Hallerwiese
Nürnberg, Germany

Karin.Becke@diakonieneuendettelsau.de

Claudia Höhne
Consultant
Department of Anaesthesiology and Intensive Care Medicine
University Hospital of Leipzig
Leipzig, Germany

claudia.hoehne@medizin.uni-leipzig.de

Michael Brackhahn
Consultant
Department of Paediatric Anaesthesia, Paediatric Intensive Care and Emergency Medicine
Paediatric Hospital 'Auf der Bult'
Hanover, Germany

Brackhahn@hka.de

Current treatment options and challenges – Dr. K. Becke

Background

An increasing number of diagnostic and treatment procedures are performed outside the operating room. Without sedation even minor procedures such as vaccination can be painful, stressful and lead to severe trauma. Sedation ensures optimal conditions for performing safe and high-quality interventions.

Children are at increased risk from the combination of analgesia and sedation, especially from respiratory complications. The recently published APRICOT study found a higher incidence of severe critical events associated with anaesthesia than previously believed (Habre et al. 2017).

Sedation and analgesia for short interventions are increasingly carried out by non-anaesthesiologists. The Paediatric Research Consortium's analysis of 50,000 sedations/anaesthetic procedures showed that only 10% were performed by paediatric anaesthesiologists (Cravero et al. 2009).

Sedation goals

The goals of paediatric sedation are to:

- Guard the patient's safety and welfare
- Minimise physical discomfort and pain for the patient
- Control anxiety, minimise psychological trauma, and maximise the potential for amnesia
- Modify behaviour and/or movement so as to allow the safe completion of the procedure (particularly important in radiology)
- Return the patient to a state in which discharge from medical/dental supervision is safe (Coté et al. 2016)

The Safetots.org initiative summarised good perioperative practice as the '10 Ns':

1. No fear
2. Normovolemia
3. Normotension
4. Normocardia
5. Normoxemia
6. Normocarbia
7. Normonatremia
8. Normoglycemia
9. Normothermia
10. No pain

Interdisciplinary framework

Hospitals should take a systematic approach to sedation by defining sedation, qualifications of the team, pre-sedation evaluation and regimes for different interventions.

Procedural sedation

The new pragmatic approach is to distinguish between two types of sedation:

- Minimal sedation or anxiolysis without compromise of cardiorespiratory or neurologic function, is appropriate for minor procedures such as inserting an IV line and making dressings.
  - o Drugs for minimal sedation or anxiolysis include
    - Midazolam
    - Single dose opioid (e.g. IN)
    - Nitrous oxide (< 50%)
    - Dexmedetomidine
- Deep sedation is equivalent to general anaesthesia, and is appropriate for radiology procedures.
  - o Drugs for deep sedation include propofol, ketamine, remifentanil, dexmedetomidine or combinations

Sedation team

Nurses, dentists and paediatricians are competent to administer minimal sedation or anxiolysis, where only SpO_2 monitoring is required.

Teams performing deep sedation must have the requisite knowledge and competencies in order to avoid respiratory adverse events. Team members will be anaesthesiologists, intensivists or emergency doctors, who have basic and advanced paediatric life support training, and can insert intravenous lines, and have bag mask ventilation skills and airway management skills to secure the airway.

Pre-sedation evaluation

Preoperative evaluation and preparation for sedation is the same as for general anaesthesia. Patients and parents need to be informed about what is going to be performed. The anaesthesiologist needs to make careful preoperative evaluation of the patient, particularly their medical history,

including difficult airway situations and comorbidities.

Fasting prior to sedation is important, with recommended fasting times as follows:

- Solids, 6 hours
- Breast milk/formula (children < 1 year), 4 hours
- As for general anaesthesia, all children should receive clear fluids for up to 2 hours before sedation

Monitoring

The minimal standards for deep sedation are ECG, BP, SpO_2 and capnography. There may also be specific prerequisites depending on the environment, e.g. telemetrics in the MRI suite.

Regimes for different interventions

Standardised interdisciplinary sedation regimes should be devised and implemented in each department, e.g. radiology, oncology, endoscopy. Measures of quality assessment and improvement should be performed continuously.

Documentation and follow-up

Sedation should be documented as for general anaesthesia. After deep sedation the patients should go to the recovery room and be monitored. There needs to be defined discharge criteria, information for patients and families on behaviour at home, and what to do in case of complications and a contact telephone number.

In-hospital paediatric sedation - areas for improvement - Prof. C Hohne

Adverse events in paediatric sedation have a prevalence of around 4.8%. To minimise the potential for adverse events, there are a number of areas where improvements are possible, including fasting times, patient monitoring and new drugs.

Fasting times

Fasting times are as for general anaesthesia. Liquids may be taken up to 2 hours before the procedure, or for up to 4 hours before in infants under 12 months. Food can be taken by children over 12 months until 6 hours before sedation. Gastric content volume is highly variable and independent of fasting time (Schmitz et al. 2011). Beach and colleagues (2016) found that nil by mouth for liquid or solids is not an independent predictor for aspiration—rather age, ASA status, comorbidities or the procedure itself were predictors. If we have a planned procedure, and it is not known if the child has fasted or not, it may not be necessary to postpone due to risk of aspiration. Current specified fasting times are safe, but are often exceeded, leaving children hungry and thirsty (Engelhardt et al. 2011). An observational study by Dennhardt and colleagues found that optimised fasting times decreased ketone body concentration and stabilised mean arterial pressure (Dennhardt et al. 2016).

Monitoring

With mild sedation, oxygen, heart rate and ventilation are monitored, and the anaesthesiologist can still communicate with the child. For deeper sedation, monitoring is as for general anaesthesia, including blood pressure, oxygen saturation and capnography. All vital signs should be recorded and documented, and age-appropriate equipment used (Coté et al. 2016).

Drugs

Drugs for sedation need to be short acting, safe, with predictable effects and keeping the airway patent. Propofol is commonly used for moderate and deep sedation, and is safe when administered by paediatric anaesthesiologists. It has a short recovery time, and if there are haemodynamic and respiratory events, these are easily treated. Careful use is advised in case of aortic or mitral stenosis/pulmonary hypertension due to the vasodilation effect (Tobias 2015). Ketamine or dexmedetomidine alone or in combination may be used either intravenously or intranasally. Dexmedetomidine could be a good alternative for patients with difficult airways. However, with the exception of propofol, most drugs are used off-label, and new drugs are needed.

A novel oral solution for paediatric sedation- Dr. Michael Brackhahn

Midazolam is used routinely for premedication in paediatric anaesthesia, but in many countries it is used off-label. Oral midazolam is used for anaesthetic premedication and for diagnostic and therapeutic procedures, e.g. sutures, IV placement, CT or MRI scans.

Oral midazolam solution is a well-known benzodiazepine with sedative, hypnotic, anxiolytic, amnesic, skeletal muscle relaxant and anticonvulsant properties, and it is an excellent alternative to drugs that require invasive administration routes. Currently available oral midazolam solutions have a bitter taste, which are poorly accepted by children.

ADV6209 is an innovative 0.2% oral midazolam formulation initially developed in 2008 through collaboration between anaesthetists and pharmacists at CHU d'Amiens-Picardie in Northern France. The objectives were to develop a more acceptable oral midazolam formulation, for use in pre-medication before general anaesthesia and moderate sedation, before and during therapeutic and diagnostic procedures. ADV6209 does not have the bitter taste of currently available preparations and so is better accepted by children. The solution has no preservative, lactose or colorants, and is currently undergoing regulatory submission in the EU.

As part of its development, ADV6029 was investigated in a phase II study involving 37 paediatric patients, who received premedication before general anaesthesia at Amiens University Hospital (Guittet et al. 2016). The sedative effect was measured after the patients received a single dose administration of ADV6209 at a mean midazolam dose of 0.27 mg/kg. The findings of the phase II study were compared to previous literature reports. In the trial satisfactory sedation was achieved in 78.4% of the patients, 30 minutes after administration of ADV6209. There was no significant difference between the overall responder rate obtained with ADV6209 and the literature findings observed with other oral midazolam formulations.

ADV6209 was well accepted by children of various ages. ADV6209 was a safe and efficacious sedative at the dose investigated. The recommended dose of ADV6029 is 0.25 mg/kg, with a maximum dose of 20mg. ■

References

For full references, please email editorial@icumanagement.org or visit https://iii.hm/de4

Matteo Parotto*
Assistant Professor
Department of Anesthesia
University of Toronto

Department of Anesthesia and
Pain Management
Toronto General Hospital

Interdepartmental Division
of Critical Care Medicine
University of Toronto

Matteo.Parotto@uhn.ca

Margaret S. Herridge
Professor
Interdepartmental Division
of Critical Care Medicine
University of Toronto

Department of Medicine
University Health Network
Toronto, Canada

* corresponding author

Outcomes after 1 week of mechanical ventilation for patients and families

We review recent findings on outcomes in adults after mechanical ventilation for one week or more in the intensive care unit, exploring both patients and their family perspectives.

Critical illness survivorship carries a burden of physical and neuropsychological disabilities (Griffiths and Jones 1999; Herridge and Cameron 2013). These determine decreased quality of life when compared to the sex- and age-matched general populations as well as increased healthcare resource utilisation (Herridge et al. 2011; Hopkins et al. 1999; Schelling et al. 2000; Weinert et al. 1997). Previous studies suggest that age (Barnato et al. 2011; Ehlenbach et al. 2010; Herridge et al. 2003), premorbid functional status and frailty (Hopkins et al. 1999; Barnato et al. 2011; Ehlenbach et al. 2010; Herridge et al. 2003; Iwashyna et al. 2010; Pandharipande et al. 2013), reason for intensive care unit (ICU) admission (Unroe et al. 2010), burden of co-morbid illness (Herridge et al. 2011; Herridge et al. 2003; Hopkins et al. 1999), and ICU length of stay (LOS) and weakness (Unroe et al. 2010; Needham et al. 2014; Carson et al. 2012) may affect recovery trajectories after ICU discharge.

However, until recently, there was a paucity of data on determinants of outcomes in adult patients who survive one week or more of mechanical ventilation (MV) in medical and surgical ICUs. The understanding of such determinants is important to critical care physicians, as it may aid patient-centred care, prognostication, education, rehabilitation and study design. In parallel, knowledge around the impact of patient trajectories after ICU on their caregivers is limited, yet fundamental. A large proportion of patients who receive prolonged MV during a stay in the ICU and survive to discharge require assistance from a caregiver 1 year after ICU discharge (Chelluri et al. 2004). Although caregiver assistance is often essential for patients, such care may have several potential negative consequences affecting physical and mental health of the caregivers (Cameron et al. 2006; Van Pelt et al. 2007; Azoulay et al. 2005).

In the past few years, the literature has provided a growing body of information in these important areas of ICU practice that can help better inform the management of patients and their caregivers.

In light of the findings from recent studies, in the present article we provide a brief review on outcomes after 1 week of mechanical ventilation for patients and families, and of the predictors for these outcomes.

Patient outcomes

Some evidence is accumulating to indicate that for patients needing ICU stays longer than 7 days, admission diagnosis and physiological illness severity may not be reliable predictors of outcome and trajectories of recovery. Researchers have suggested that this might be the reflection of a transition to a different disease state, such as persistent critical illness (Iwashyna et al. 2016), or may reflect the fundamental importance of pre-ICU illness trajectory in determining post-ICU outcome.

Recently, prospective data became available from the RECOVER Program. This initiative began in 2007 in collaboration with the Canadian Critical Care Trials Group, and was focused on risk strata post ICU (Herridge et al. 2016). The Towards RECOVER study, the first step of this multi-phase project, evaluated a multi-centre Canadian cohort of 391 medical/surgical ICU patients, who received one week or more of MV, at 7 days, 3, 6, and 12 months after ICU discharge. Patients in this cohort had a mean age of 58 years; 42% were female. The majority of them lived at home and independently prior to their critical illness. The median Acute Physiology and Chronic Health Evaluation (APACHE) II was 22 and median Multiple Organ Dysfunction score (MODS) on day 7 of MV was 6. Seven days after ICU discharge, all patients reported weakness and functional limitations, and the majority were unable to walk. Depressive symptoms were common and several patients (23%) reported features of post-traumatic stress disorder at 3 months post ICU discharge, which persisted at 1 year in the majority of cases.

A recursive partitioning model showed that disability is determined by age and ICU length of stay (LOS) based on the Functional Independence Measure (FIM) at 7 days post ICU discharge, independent of admitting diagnosis and severity of illness. Four distinct disability risk groups were identified [Young Short LOS (age <42 years, ICU stay <2 weeks); Mixed-age Variable LOS (≥42 years, <2 weeks

and ≤45 years, ≥2 weeks); Older Long LOS (46-66 years, ≥2 weeks), and Oldest Long LOS (> 66 years, ≥14 days)]. These groups were characterised by different outcomes and post-ICU healthcare utilisation, with increasing disability from the Young Short LOS to the Oldest Long LOS. In the latter group, only 19% were discharged home directly from hospital, and over one-third required hospital readmission in the year after ICU discharge. Forty percent of this group died within the first 12 months after ICU discharge, and the surviving patients had severe and persistent functional dependency. Cognitive dysfunction, including problem solving and memory, was affected uniformly across risk groups.

Iwashyna and colleagues conducted a large retrospective, population-based observational study on over 1 million patients from 182 ICUs across Australia and New Zealand (Iwashyna et al. 2016). They found that among patients still in ICU, admission diagnosis and physiological derangements, which accurately predicted outcome on admission, progressively lost their predictive ability after 10 days, and no longer predicted outcome more accurately than did simple antecedent patient characteristics such as age, sex and chronic health status. Patients who were still in the ICU after one week from the onset of acute critical illness experienced higher mortality and resource utilisation, and had a much lower chance of returning directly to home at hospital discharge. In their retrospective cohort study of a random sample of 35,000 Medicare beneficiaries older than 65 years old, who received ICU care and survived to hospital discharge, Moitra et al. showed that for each day beyond 7 days in the ICU there was an increased risk of death by 1 year, irrespective of the need for MV (Moitra et al. 2016). Altogether, data from these recent studies may suggest that a complex interaction of specific physiological changes determined by acute illness with prolonged ICU stay coupled with the patient's prior functional and health status determine reserve and resiliencies that dictate outcomes and the trajectory of recovery.

The MEND-ICU Program, a pilot study led by Drs. Batt and Dos Santos, in collaboration with the RECOVER Program, (Dos Santos et al. 2016) focused on the determinants of muscle dysfunction and differential resilience and disability after critical illness. The authors recruited patients with the goal to delineate cellular mechanisms underlying long-term persistence of weakness in ICU survivors. Assessments were conducted at 7 days and 6 months after ICU discharge, including motor functional capacity, quadriceps size, strength, voluntary contractile capacity, electromyography, nerve conduction studies, and vastus lateralis biopsies for histologic, cellular and molecular analyses. The authors concluded that long-term weakness in ICU survivors results from heterogeneous muscle pathophysiology with variable combinations of muscle atrophy and impaired contractile capacity. These findings are associated with decreased satellite cell content and compromised muscle regrowth, suggestive of impaired regenerative capacity.

> **critically ill patients with similar degrees of physiologic derangement may have very disparate trajectories of resolution of organ dysfunction and recovery**

Caregiver outcomes

The experience of caregivers for critically ill patients is equally a life transformative one. They often present mood disorders, such as depression and post-traumatic stress disorder (Azoulay et al. 2005), and these may also affect their capability to care for the family member, whose outcomes could hence be compromised (Herridge and Cameron 2013).

Choi and colleagues prospectively studied caregivers of critically ill patients who received MV for at least 7 days (Choi et al. 2011). The family caregivers completed follow-up at 1 and 6 months after discharge from the intensive care unit. Although limited by the relatively small sample size, the findings of this study highlighted the physical and psychological burden experienced by caregivers, and reported that 20% of caregivers perceived moderate or greater restrictions in nearly all areas of daily life, particularly the areas related to social life or personal recreation. These suggest the importance that interventions designed to enhance coping, decrease social isolation, and improve patients' functional status may have in assisting this vulnerable and often neglected population.

In parallel to the patient data, the RECOVER Program also described detailed health outcomes in caregivers of critically ill patients, identifying subgroups of caregivers with distinct health trajectories and assessing variables associated with poor caregiver outcomes (Cameron et al. 2016). The parallel caregiver cohort of the RECOVER Program enrolled family members or friends who were primarily responsible for providing or coordinating care after hospital discharge, without financial compensation, to patients who had received at least 7 days of MV and were discharged alive from ICU. The caregivers' mean age was 53 years, with the majority being women, and almost two-thirds caring for a spouse.

This study showed that mental health was severely affected in the cohort, with depressive symptoms present in a large percentage of caregivers (67% initially and 43% at one year), and although in the majority of cases depressive symptoms decreased over time, in a subgroup (16%) no signs of improvement were recorded. Conversely, physical health appeared unaffected and similar to population norms.

Interestingly, and consistently with findings from previous pilot data (Choi et al. 2012), no patient variables were associated with caregiver outcomes. Indeed, no patient demographic and clinical characteristics nor changes in patient functional and psychological outcomes over time appear to correlate with caregiver outcomes.

Instead, Cameron and colleagues identified how the characteristics of the caregiver and the caregiving situation were important determinants of caregiver outcomes during the follow-up period. The variables that were significantly associated with worse mental health outcomes include younger age, greater effect of patient care on other activities, less social support, less sense of control over life and less personal growth.

Summary and conclusions

Novel data have recently become available that describe patient outcomes after 1 week or more in the ICU. Survivors have important physical

and mental health consequences, independent of admitting diagnosis and severity of illness (Herridge et al. 2016; Moitra et al. 2016; Iwashyna et al. 2016). Long-term weakness following resolution of critical illness is associated with variable combinations of muscle atrophy and impaired voluntary contractile capacity, which result from impaired regenerative capacity. Muscle biology can be durably and even definitely altered by critical illness (Dos Santos et al. 2016).

A new perspective emerges, suggesting that critically ill patients with similar degrees of physiologic derangement may have very disparate trajectories of resolution of organ dysfunction and recovery, that appear unrelated to the admitting diagnosis or severity of disease, and fundamentally determined by their age and ICU LOS and pre-ICU health status. Hence, physiologic definitions such as those currently in use for Acute Respiratory Distress Syndrome (ARDS) (ARDS Definition Task Force 2012) or sepsis (Shankar-Hari et al. 2016) may not assist in defining the longer-term prognosis of these patients. Furthermore, as the duration of ICU stay increases, patients may transition to a different disease state in which they continue to accrue disability over time, which may be referred to as persistent or chronic critical illness, characterised by increased 1 year mortality, resource utilisation and inability to return home (Iwashyna et al. 2016; Moitra et al. 2016).

This novel information can help inform goals of care discussions, discharge planning, rehabilitation and long-term expectations for recovery and functional autonomy. Future studies are needed to better characterise individual responses to critical illness, their resilience and potential for repair, and whether different interventions should be designed for different disability risk groups to help improve patient outcomes. The delineation of the role played by functional status pre-ICU in the trajectory of recovery, and how it relates to the response to prolonged ICU stay is of central importance, and perhaps in particular for elderly patients (Ferrante et al. 2015).

In parallel to a better understanding of the trajectory of recovery after 1 week of mechanical ventilation, we are learning how critical illness affects the entire family. Caregivers' mental health is severely affected, and the identification of those more vulnerable to such consequences may inform the provision of additional support/resources, as well as assist in the design of future studies aimed at assessing the effects of different interventions to improve caregiver outcomes.

In critical illness, as in all aspects of medicine, considering the family as a whole is fundamental and central to effective and compassionate care delivery (Wittenberg and Prosser 2016).

Conflict of interest

Matteo Parotto declares that he has no conflict of interest. Margaret Herridge declares that she has no conflict of interest.

Supported by: Canadian Institutes of Health Research, Ontario Ministry of Health Innovation Fund; University of Toronto-Department of Medicine Challenge Integration Fund; the John MacNaughton Family Fund, the Jason Tham and Andrea Chan Family fund and the Don and Jane Luck Family Fund.

Acknowledgements

We are indebted to the patients and their families for their willingness to participate in the RECOVER Program and for graciously donating their time to this research program.

The authors are extremely grateful to the Canadian Institutes of Health Research, Ontario Ministry of Health Innovation Fund; University of Toronto-Department of Medicine Challenge Integration Fund; the John MacNaughton Family Fund, the Jason Tham and Andrea Chan Family fund and the Don and Jane Luck Family Fund for their very generous support of this programme of research.

The authors also thank the RECOVER Research Coordinators at each of our sites across Canada. Paulina Farias from University Health Network (Toronto); Cheryl Ethier, Maedean Brown, Brittany Giacomino and Sumesh Shah from Mount Sinai Hospital (Toronto); Orla Smith, Yoon Lee, Kerri Porretta, Julia Lee and Melissa Wang from St. Michael's Hospital (Toronto); Nicole Marinoff, Jane Wang, Derek Parsotam and Ashwati Raghunath from Sunnybrook Health Sciences Centre (Toronto); Andrea Tkaczyk and France Clarke from St. Joseph's Healthcare (Hamilton); Mary-Jo Lewis, Tracey McArdle and Brigette Gomes from Ottawa Hospital Civic Campus (Ottawa); Johanne Harvey from Hôpital Maisonneuve-Rosemont (Montreal); Chantal Langevin, Karine Grondi, Joanie Lacasse-Bedard and Eugenie Pinsonnault from the University Hospital Centre of Sherbrooke (Quebec); Lynda Lazosky and Ellen Woo from St. Paul's Hospital (British Columbia)

Abbreviations

ICU intensive care unit
LOS length of stay
MV mechanical ventilation

References

ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT et al. (2012) Acute respiratory distress syndrome: the Berlin Definition. JAMA, 307: 2526-33.

Azoulay E, Pochard F, Kentish-Barnes N et al. (2005) Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med, 171: 987-94.

Barnato AE, Albert SM, Angus DC et al. (2011) Disability among elderly survivors of mechanical ventilation. Am J Respir Crit Care Med, 183: 1037-42.

Cameron JI, Chu LM, Matte A et al. for the RECOVER Program Investigators (Phase 1: towards RECOVER.; Canadian Critical Care Trials Group. (2016) One-year outcomes in caregivers of critically ill patients. N Engl J Med, 374(19): 1831-41.

Cameron JI, Herridge MS, Tansey CM et al. (2006) Well-being in informal caregivers of survivors of acute respiratory distress syndrome. Crit Care Med, 34: 81-6.

Carson SS, Kahn JM, Hough CL et al. (2012) A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. Crit Care Med, 40: 1171-6.

Chelluri L, Im KA, Belle SH et al. (2004) Long-term mortality and quality of life after prolonged mechanical ventilation. Crit Care Med, 32: 61-9.

Choi J, Donahoe MP, Zullo TG et al. (2011) Caregivers of the chronically critically ill after discharge from the intensive care unit: six months' experience. Am J Crit Care, 20: 12–23.

Choi J, Sherwood PR, Schulz R et al. (2012) Patterns of depressive symptoms in caregivers of mechanically ventilated critically ill adults from intensive care unit admission to 2 months postintensive care unit discharge: a pilot study. Crit Care Med, 40: 1546-53.

Dos Santos C, Hussain SN, Mathur S et al., MEND ICU Group.; RECOVER Program Investigators.; Canadian Critical Care Translational Biology Group. (2016) Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med, 194: 821-30.

Ehlenbach WJ, Hough CL, Crane PK et al. (2010) Association between acute care and critical illness hospitalization and cognitive function in older adults. JAMA, 303: 763-70.

Ferrante LE, Pisani MA, Murphy TE et al. (2015) Functional trajectories among older persons before and after critical illness. JAMA Intern Med, 175: 523-9.

Griffiths RD, Jones C (1999) Recovery from intensive care. BMJ, 319: 427-9.

Herridge M, Cameron JI (2013) Disability after critical illness. N Engl J Med, 369: 1367-9.

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

Patient Temperature Management Solutions in the Adult ICU

Blanketrol® III & Kool-Kit®

An effective method for Whole Body Cooling

Therapeutic Hypothermia takes temperature management to the next degree by prescribing precise temperatures in order to manage the metabolic functions of the body. Cincinnati Sub-Zero understands the importance of cooling quickly and accurately.

This temperature management system provides an effective alternative to traditional patient cooling techniques. Our revolutionary system combines the SMART technology of the Blanketrol® III with the body surface area coverage of the Kool-Kit® for a non-invasive whole-body temperature management solution.

A GENTHERM COMPANY

www.cszmedical.com

10203

Continuing rehabilitation after intensive care unit discharge

Opportunities for technology and innovation

Sara Evans
Senior Staff Nurse
Intensive Care Unit
Royal Berkshire Hospital
Reading, UK

sara.evans@royalberkshire.nhs.uk

Dhaneesha Navin Sannasgala Senaratne
CT2 in Anaesthesia
Intensive Care Unit
Royal Berkshire Hospital
Reading, UK

dns.senaratne@gmail.com

Carl Waldmann
Consultant in Anaesthesia and Critical Care Medicine
Intensive Care Unit
Royal Berkshire Hospital
Reading, UK

carl.waldmann@royalberkshire.nhs.uk

This article discusses technological innovations that promote survival and enhance recovery, starting within the ICU with developments in ventilation, sedation, early mobility and ICU design. Post-ICU, the establishment of follow-up services is discussed, as are initiatives for sharing patient information to achieve better continuity of care and the novel concept of teleclinics. Specific issues after ICU with sexual function and driving are also addressed. New developments for the future are also outlined.

The Kings Fund in the UK published a seminal report in 1989 about intensive care unit (ICU) services, acknowledging for the first time: "There is more to life than measuring death" (Kings Fund 1989). Since then morbidity after ICU has been viewed as an outcome, and much more has been learnt about what is now known as post-intensive care syndrome (PICS) (Needham et al. 2012), a clinical syndrome that encompasses a constellation of physical symptoms (e.g. muscle weakness, fatigue, reduced mobility), cognitive dysfunction (e.g. impaired memory, reduced concentration) and psychological symptoms (e.g. depression, anxiety, sleep disturbance). Such issues are commonplace; for example, a systematic review found that ICU-acquired weakness affected 32% of those ventilated for 7 days (Appleton et al. 2015), whilst ICU survivors report lower physical health-related quality of life than the general population (Cuthbertson et al. 2013). Similarly, 20% of ARDS patients show signs of impaired cognition six years after discharge (Harvey et al. 2016). Furthermore, a meta-analysis of post-traumatic stress disorder (PTSD) in ICU survivors showed a rate of 20% at 1 year post-discharge (Parker et al. 2015), and 44% of those discharged were found to be anxious and depressed (Griffiths et al. 2013). This syndrome can extend to families of those who have been in ICU, who also exhibit signs of psychological distress (PICS Family; PICS-F) (Davidson et al. 2012) and the effects can last for years, especially if the ICU survivor has a poor quality of life (Mikkelsen et al. 2017). The consequences of both PICS and PICS-F extend beyond the realms of immediate physical and mental health to economic and social dysfunction, as those affected struggle to return to work or education, or stop work to care for their loved one (Griffiths et al. 2013).

All this evidence demonstrates that the road to a full recovery and return of baseline function following critical illness and ICU admission is long, and is filled with challenges. Innovation in the implementation of systems and the development of new technology can help optimise patient outcomes and experiences. The changes that affect our cohort of patients are occurring simultaneously within and outside the ICU.

Innovation and technology within the ICU

Recovery from ICU begins in ICU. Guidance from the ICU Delirium and Cognitive Impairment Study Group (2017) and by Barr et al. (2013) outlines the importance of effective management of pain, agitation and delirium. By achieving this, oversedation can be avoided, which subsequently reduces ICU-acquired delirium and weakness (Vasilevskis et al. 2010). The ABCDEF bundle has been developed to help guide healthcare professionals; it consists of **A**ssessing/managing pain, spontaneous awakening/**B**reathing trials (sedation holds), **C**hoice of sedation, assessing/managing **D**elirium, **E**arly mobility/**E**xercise, and **F**amily involvement (ICU Delirium and Cognitive Impairment Study Group 2017). Balas et al. (2014) measured the impact of this bundle and found ventilation duration was reduced by three days and delirium duration was reduced by one day.

Weaning

Advances in ICU equipment and pharmacology have also changed practice. For example, new closed loop ventilator systems

with automatic weaning (e.g. IntelliVent® [Hamilton Medical], SmartCare™ [Draeger Medical]) also purport to reduce total ventilator days. A Cochrane review showed SmartCare™ decreased weaning time and reduced length of ICU stay in critically ill adults (Burns et al. 2014). Similarly, when considering sedation Shehabi et al. (2012) found that deep sedation in the first 48 hours of admission was related to number of ventilator days (i.e. deeper initial sedation led to delayed extubation). Alternative sedatives (e.g. dexmedetomidine) have been shown to reduce ventilator days when compared to traditional sedatives (Riker et al. 2009) and are increasingly being used in clinical practice.

Communication

One of the key frustrations of ICU patients is the inability to communicate effectively with staff and family members, and advances in technology have real potential to make this experience smoother. For example, devices that allow patients to select pictures that then vocalise certain phrases, or eye-tracking devices that allow patients to control a mouse cursor can allow quite unwell patients to communicate (ten Hoorn et al. 2016). In a small study, the ability to communicate was shown to reduce drop-out depression and anxiety (Maringelli et al. 2013). However, there is a need to make this technology personal to the individual; Stayt et al. (2015) identified the risk that novel technology could potentially be dehumanising and divert attention from the individual's psychosocial needs. Clearly a balance needs to be achieved but there are significant gains that could be made.

Early mobilisation

Early mobilisation is becoming an important standard of care and is often matched with alternative strategies to maintain muscle strength and function. A systematic review by Adler and Malone (2012) found early mobilisation to be safe and provide a significant benefit in terms of functional outcomes. Similarly, early physiotherapy was found to reduce the duration of ventilation and delirium, and led to better functional outcomes on hospital discharge (Schweickert et al. 2009). Scores in the the Chelsea Critical Care Physical Assessment (CPAx) tool, used to measure physical morbidity in ICU, have a clear association with discharge destination from hospital (Corner et al. 2014). This is significant in planning rehabilitation after critical illness.

"A universal ICU recovery programme (akin to cardiac rehabilitation following myocardial infarction) is lacking"

Motor-assisted movement therapy devices (e.g. MOTOmed® [Medimotion, Pencader, UK]) offer a range of exercises that may be appropriate even for sedated patients, helping to maintain muscle strength and function (Needham et al. 2009). Such devices have demonstrated improved six-minute walk distance and self-reported physical function by hospital discharge, though this could be ascribed to the longer physiotherapy sessions as opposed to the technology itself (Needham et al. 2009). The Mollii suit™ (in development by Inerventions, Danderyd, Sweden) is designed to help spasticity using transcutaneous electrical nerve stimulation (TENS) technology to develop muscle movement, control and tone. There is minimal peer-reviewed evidence to support benefit of this system over existing treatments but the UK's National Institute for Health and Care Excellence (NICE) has issued an innovation briefing (NICE 2017) and is monitoring its development. It is unclear whether this technology is suitable for post-ICU patients, though if benefit is demonstrated in other populations then further research into the post-ICU cohort may be warranted.

Environment

Technology may also play a part in the design of new ICU environments. For example, cycled lighting systems that aim to minimise disruption to natural circadian rhythms are associated with a more positive patient experience (Engwall et al. 2015), though objective assessment of benefit is less evident (Engwall et al. 2017). Smart alarms, that combine multiple parameters to reduce false alarms (da Silva et al. 2012), and sound-absorbing materials (Johansson et al. 2016) have both been proposed. The Helen Hamlyn Centre for Design at the Royal College of Art is developing Senso, an app that aids orientation to time and helps to create routines for patients, for example by providing relaxing music and images at sleep time with the aim of promoting sleep and reducing delirium/distress, which in turn has the potential to improve psychological outcome (Meldaikyte, pers. comm. 2016). All of these features may make the ICU environment less alien.

Innovation and technology after the ICU

We are increasingly aware of the long-term consequences of critical illness and ICU admission. To this effect ICU teams are increasingly involved in the long-term care of patients following ICU and hospital discharge. Although ICU follow-up clinics have existed in the UK since the early 1990s their implementation is variable; in 2006 only 30% of units (Griffiths et al. 2006a) had a follow up service, whilst in 2014 only 27.3% of ICUs offered a clinic-based follow-up at 2-3 months post-discharge (Connolly et al. 2014). These can often be used to identify patient/familial issues and coordinate their ongoing medical care and rehabilitation (de la Cerda 2013).

The Royal Brompton & Harefield NHS Foundation Trust has developed a novel web-based pathway called *Hospital to Home*, which is used for all adult patients who have received ECMO (**hospitaltohome.nhs.uk/adult**). This platform allows sharing of patient information across different teams on different sites, from the base time at the Royal Brompton to the repatriation team to the outpatient follow-up teams. It goes some way to ensuring better continuity of care for these complex patients, and there are indications that this joined-up care can also lead to significant resource savings (Langley et al. 2017).

Former ICU patients may have specific physical health consequences of their ICU admission. For example, in patients who

received a tracheostomy (up to 24% of those requiring mechanical ventilation; Raimondi et al. 2017), tracheal stenosis is a recognised complication. Advances in MRI/CT technology can be used to identify and follow up such patients, though information on morbidity from this is lacking (Veenith et al. 2008). Similarly, sexual dysfunction is common in post-ICU patients, with up to 45% of former patients reporting problems (Quinlan et al. 2001). Erectile dysfunction is an area of active technological development, with innovation in external penile support devices, vibrators, low-intensity extracorporeal shockwave treatments and impulse magnetic field therapies (Stein et al. 2014). Both men and women may also require referral for psychosexual therapy.

A universal ICU recovery programme (akin to cardiac rehabilitation following myocardial infarction) is lacking. However, some attempts have been made to investigate possible beneficial components. Jackson et al. (2012) performed a pilot study of a programme comprising both cognitive and physical rehabilitation lasting 12 weeks. New technologies (e.g. video calls) formed a central component alongside established follow-up practices such as home visits. Furthermore, they used videos of patients doing physical and functional activities in their homes and "motivational" phone calls. The authors believe that this was the first initiative using such technology with ICU survivors, and noted the benefits of being able to reach those who may be too debilitated to reach hospital, and those who may live too remotely to return to the hospital. This allowed access to specialists that these individuals may not otherwise have had, as well as potentially reducing both direct costs (e.g. costs of hospital appointments, hospital transport) and indirect costs (by reducing the socioeconomic burden of health). The researchers concluded planned physical and mental activities are potentially beneficial in this population and need further research.

The ability to drive is often an important target for patients in their recovery. However, it is also an extremely useful marker of progress for healthcare professionals, as it requires simultaneous and interdependent physical and cognitive functioning. Advances in technology are making adaptions easier and cheaper in normal vehicles allowing patients to overcome specific physical difficulties. Programmes like the Motability Scheme (**motability.co.uk**) allow patients access to facilities to develop their own independence. This has been shown to improve independence and confidence (Meyer & Waldmann 2015).

Innovation in change

The above demonstrates numerous examples of how innovation and technology have influenced specific components of the ICU recovery pathway. However, the processes by which we identify and deliver changes themselves are also evolving and improving over time. For example, Locock et al. (2014) demonstrated how the Accelerated Experience Based Co-Design (AECBD) approach, which involves using patient experience narratives (often in the form of videos) to facilitate multilateral discussions between patients and healthcare professions, can be used to drive patient-centred service improvements. They demonstrated that the process is welcomed by both staff and patients, and the co-design approach puts patients at the heart of service development. We have used a similar strategy in our own ICU on several occasions; for example, our "Voiceless" project identified patient frustrations with their difficulties in communication, and has led to the development of materials and leaflets that form a starting point in educating staff, patients and families and ultimately ensuring more effective interaction.

Conclusion

As we have seen, there are many opportunities for innovation and the introduction of new technology throughout the healthcare journey for the ICU patient. These may address physical, psychological and cognitive factors relating to individual patients and their families, or may be used to implement wider service level improvements. Nevertheless, as new technology is developed, new opportunities for improvement arise. There is plenty of scope for continued improvement in the future.

Conflict of interest

Sara Evans has attended study days paid for by Orion Pharma (dexmedetomidine). Dhaneesha Navin Sannasgala Senaratne declares that he has no conflict of interest. Carl Waldmann has received travel expenses and an honorarium from Orion Pharma to chair a study day. ■

References

Adler J, Malone D (2012) Early mobilization in the intensive care unit: a systematic review. Cardiopulm Phys Ther J, 23(1): 5-13.

Appleton RTD, Kinsella J, Quasim T (2015) The incidence of intensive care unit-acquired weakness syndromes: a systematic review. Journal of the Intensive Care Society 16(2): 126–36.

Balas MC, Vasilevskis EE, Olsen KM et al. (2014) Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobilisation bundle. Crit Care Med, 42(5): 1024-36.

Barr J, Fraser GL , Puntillo K et al. (2013) Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med, 41(1): 263-306.

Burns KEA, Lellouche F, Nisenbaum R et al. (2014) Automated weaning and SBT systems versus non-automated weaning strategies for weaning time in invasively ventilated critically ill adults. Cochrane Database Syst Rev, 9(9): CD008638.

Connolly B, Douiri A, Steier J et al. (2014) A UK survey of rehabilitation following critical illness: implementation of NICE Clinical Guidance 83 (CG83) following hospital discharge. BMJ Open, 4(5): e004963.

Corner EJ, Soni N, Handy JM et al. (2014) Construct validity of the Chelsea critical care physical assessment tool: an observational study of recovery from critical illness. Crit Care, 18(2): R55.

Cuthbertson B, Elders A, Hall S, et al. (2013) Mortality and quality of life in the five years after severe sepsis. Crit Care, 17(2): R70.

da Silva RCL, Fittipaldi A, Louro TQ et al. (2012) Alarms in intensive care units and its implications for the patient comfort: integrative review. J Nurs UFPE 6(7): 2800-7.

Davidson JE, Jones C, Bienvenu OJ (2012) Family response to critical illness: post-intensive care syndrome-family. Crit Care Med 40(2): 618–24.

de la Cerda G (2013) Implementation of an ICU follow-up clinic: outcomes and patient satisfaction after 1 year. Crit Care 17(Suppl 2): P538.

Engwall M, Fridh I, Johansson L et al. (2015) Lighting, sleep and circadian rhythm: an intervention study in the intensive care unit. Intensive Crit Care Nurs, 31(6): 325–35.

Engwall M, Fridh I, Jutengren G et al. (2017) The effect of cycled lighting in the intensive care unit on sleep, activity and physiological parameters: a pilot study. Intensive Crit Care Nurs, 41: 26-32.

Griffiths JA, Barber VS, Cuthbertson BH et al. (2006a) A national survey of intensive care follow-up clinics. Anaesthesia, 61(10): 950–5.

Griffiths J, Hatch RA, Bishop J et al. (2013) An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care, 17(3): R100.

Harvey MA, Davidson JE (2016) Postintensive care syndrome: right care, right now...and later. Crit Care Med, 44(2): 381-5.

ICU Delirium and Cognitive Impairment Study Group (2017) Delirium prevention and safety: starting with the ABCDEF's. [Accessed:04 June 2017]. Available from icudelirium.org/medicalprofessionals.html

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

LIVES 2018

31ST ANNUAL CONGRESS

PARIS 20-24 OCTOBER

PALAIS DES CONGRES

Idelette Nutma-Bade
Sepsis en daarna, education and guidance
Former sepsis patient, former nurse
Author of *Sepsis and afterwards*
Experience expert
Member of the FCIC-foundation
The Hague, the Netherlands

nutma@sepsis-en-daarna.nl

sepsis-en-daarna.nl/english

The hidden faces of sepsis, what do they tell us?

Focal points for improving patient outcome

Based on the patients' perspective Nutma sheds light on the hidden faces of sepsis, calling for more expertise on sepsis sequelae. She also offers recommendations to improve recovery and outcome.

It wasn't until 2007, after my illness that: *"I came to understand the extensive process of recovery after critical illness. Moreover, I came to realise that the need for explanation, support and advice, as well as the importance of providing the patient with a good start of the recovery process, was seriously underestimated. Having been a former nurse, I considered this an important eye opener" (Nutma 2016).*

Obviously, I was enormously grateful for having been given a second chance. When my recovery came to a standstill at a certain point, I learned that survival 'in itself' wasn't sufficient to measure 'outcome'. I'm very happy that the patient's perspective of quality of life is being taken into account more and more.

Sepsis: a critical illness in disguise

In 2007 I experienced the thin line between life and death caused by sepsis. I fell ill due to a septic shock, and spent 5 days in ICU. I was in critical condition and my family was informed that "it could go either way", leaving them between hope and fear. Fortunately, thank God, I turned the corner after having been ventilated for a few days. Sepsis is incredibly sneaky. Without warning and seeming to resemble the flu, sepsis strikes like lightning, devastating both you and your loved ones. In a few hours' time I went into shock and developed acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC), the meaning of which comes close to **D**eath **I**s **C**oming.

Earlier that morning, just before ICU admission, antibiotic IV treatment because of pneumonia had already started. I tried to make sense of it all: how did my body lose control? It felt like some supernatural force was pushing me over the edge…. It started with dizziness when walking to the toilet, and soon it felt like my legs went wobbly. I made it back to bed just in time and called for the nurse. It became clear that I was very hypotensive. Shortly after that my feet and hands had turned ice-cold and I felt my heart beating very fast. I realised that I was going into shock. In less than 15 minutes my shortness of breath worsened and as I coughed, my mouth filled with bloody mucus and fluid. For a moment I was caught by the very fear of dying, and I thank God there was an ICU to turn to: it saved my life.

> "the struggle *for* life had turned into the struggle *with* life"

Being a nurse at the time, I tried to get a hold on things. The first few hours after my transfer to ICU I stayed very alert, and every now and again I looked over my shoulder on the monitor to see if my blood pressure was rising. It wasn't…. Sepsis, however, never crossed my mind! During my nursing education the word sepsis had been mentioned with regard to a complication of a wound infection or a peritonitis. Never ever had it been referred to as the systemic, dysregulated host response or organ dysfunction that was making my body react in this life-threatening way. Eventually I had to let go, due to exhaustion. Breathing was hardly possible, and after a moment of saying goodbye—'for better or for worse'—I was given ventilatory support. Sepsis nearly killed me, but no one ever mentioned the word…. A few months after my discharge I noticed the word sepsis in my medical record.

As said earlier, sepsis really caught me by surprise. Many patients don't realise what's going on, because the brain has already lost control. As a matter of fact, when patients do stay alert and experience life slipping through their fingers, they often don't get the chance to fully realise the impact either, because intubation makes sedation necessary. On top of all this, lots of patients don't realise 'what hit them', because, just like me, they hadn't been informed. Hence it became my mission to communicate about sepsis and to literally spread the word. Fact is, that even when patients are not admitted to the ICU (with treatment sometimes carried out under the supervision of an ICU physician) sepsis remains a critical illness. Actually, it seems to be the most common critical illness outside the ICU, for one main reason: sepsis is not often promptly diagnosed at the general ward. There's one more important aspect of disguise: when things go wrong in terms of prompt diagnosis and consistent implementation of protocols, sepsis is generally referred to as 'a complication', whereas it should actually be regarded as a calamity. The report on 'collateral damage in Dutch hospitals', published in 2007 (de Bruijne et al. 2007), led to the Security Management System implementation in hospitals, including protocols of the Surviving Sepsis Campaign. The importance of compliance was illustrated by van Zanten et al. showing a decline in the mortality rate of 16.7% (van Zanten et al. 2014). When it comes to consistent compliance and alertness, a lot of work still has to be done in hospitals and other settings, in the Netherlands, but in the rest of the world as well.

Recovery after sepsis and critical illness: from no man's land to a mission

- Given the fact that sepsis is a critical illness in disguise, extra effort is also needed to spot it proactively, including concentrating funds and scientific research to develop biomarkers.
- Raising the red flag on sepsis remains very important, just as important as communicating the word 'sepsis'.
- The same applies to creating more awareness of long term sequelae, although significant progress is being made by the Global Sepsis Alliance and many others.

My recovery took a long time and there was no aftercare whatsoever, nor information about what to expect and how to cope. It was also hard for my husband and children. My energy level was terribly low. I was readmitted three times because of an infection during the first few years, and I had problems with 'ordinary' things like planning, multitasking, remembering appointments, etc. Mentally I suffered from mood swings, a short fuse, and the quest for the explanation of the 'void'; I had no factual memories of the crisis I'd gone through. Actually, the struggle *for* life had turned into the struggle *with* life. Nowadays we know that critically ill sepsis patients are more likely to develop PTSD (Johns Hopkins Medicine 2013). Fortunately, the definition of post-intensive care syndrome (PICS) has highlighted the impact of critical illness in general (Needham et al. 2012). At the time, however, I blamed myself for having these feelings. Finally, after 8 months I found some fellow-sufferers. They also felt like they had been dropped in no man's land: deserted and facing rehabilitation all alone.

Eventually, having gained strength from complementary medicine, I decided to assemble all the information on sepsis and recovery after critical illness I could find, and write a book about it. Moreover, it triggered me to turn my mission into a new job: teaching, giving lectures, information and guidance, from the patient's perspective.

I sincerely hope *Sepsis and Afterwards* provides former patients, relatives and professionals from all over the world with a better understanding of the impact of sepsis and all that may be helpful during recovery.
Information about the book:
https://www.sepsis-en-daarna.nl/english

The hidden faces of sepsis – some focal points

Sepsis leaves a trail of devastation to many survivors and/or relatives. A few months ago I received a phone call from a woman whose sister had just passed away in ICU, due to sepsis. She told me that in a few days' time her sisters' legs had turned purple and black, and how she had witnessed her sister literally

leave this life bit by bit. It's terrifying and one of the horrible physical faces of sepsis, causing death or great *visible* impact due to disseminated intravascular coagulation (DIC). However, I'd like to shed some light on the more invisible, let's say *hidden* physical faces of sepsis: neuropathic disorders, neurocognitive sequelae and the effects on the immune system.

An important aspect of my job is to provide guidance to former patients (and/or their relatives), and it strikes me how often they report some form of neuropathy. This also applies to those who were not admitted to the ICU (meaning they were not ventilated and sedated), emphasising how sepsis itself can affect the peripheral nerve system. They may suffer from tingling, pain or even numbness. When these symptoms occur during and after ICU admission they are described as ICU-acquired weakness, but actually this expression doesn't cover the sensory aspects mentioned above. Critical illness neuropathy is a comprehensive expression for various disruptions of the nerves. This may also include autonomic dysregulation (as reported by some clients), combined with hypersensitivity to all kinds of stimuli, together with an auto-immune disease or a hyperactive immune system in general. This suggests a possible (complex) link and interaction between the brain/the central nerve system and the immune system. Many of these patients are confronted with the knowledge gap with regard to these after effects, because the expertise about sepsis among physicians is often limited to the acute phase of the illness.

> A (research) centre specialised in sepsis sequelae would really be a major step forward.

As to the neurocognitive sequelae, it is important to realise that sepsis is an independent risk factor for delirium, making patients vulnerable to neurocognitive disorder: they are facing problems with their short-term memory, mental processing speed and multitasking, and returning to work. Smith and Meyfroidt stated that "the brain is always in the line of fire" and that:

> *"a brain-oriented approach should be a unifying concept in the management of all critically ill patients" (Smith and Meyfroidt 2017).*

> More focus on neurocognitive rehabilitation(facilities) is needed

Protecting the brain is reducing neurocognitive sequelae and the effect on the immune system as well. What applies to the brain applies to PICS in general: you don't have to repair what can be protected and secured. Furthermore, especially after sepsis, the immune system is totally out of balance, giving way to all kinds of 'intruders', among other things, due to a heavily disturbed intestinal flora.

> *"According to a study published in the Journal of Hospital Medicine, about one-third of the survivors of sepsis or septic shock were readmitted within 30 days (Zilberberg et al. 2015). This all lays a heavy burden on the lives of the survivors and their family members, but on society and healthcare as well" (Nutma 2016).*

And who shows those concerned the way to build up their immune competence again?

> Patients should be provided with recovery tools to build up their immune competence.

In organising the workshop 'Recovery after sepsis' I try to make a contribution and give tips about good nutrition and dietary supplements which I found to be very helpful myself.

Conclusion

Serious attention to rehabilitation right from the start can make the difference between the downward spiral and climbing up. Fortunately the general focus on the impact of critical illness and ICU admission (which concerns many sepsis patients) has improved. Quoting *Sepsis and afterwards:*

> *"Investing in getting the ex-patient in better shape and teaching how to deal with impairments can mean a lot in terms of prevention. The so-called Balance Training for adult former ICU-patients was started up in the Netherlands in 2016, initiated by Hanneke Oonk, "Gezondheidszorgcoach" (health care coach)," together with the author of this article. "It supports survivors in dealing with long-term sequelae, by means of mindfulness, peer support and psycho education, aiming at (re)gaining the balance in body and life. [….] 'Family and Patient Centred Intensive Care' (FCIC) was founded in the Netherlands in 2015, aiming at reducing the impact of ICU care. This foundation seeks to combine expertise and experience of (health care) professionals, researchers and former patients and relatives" (Nutma 2016).*

Still, aftercare tailor made for the needs of sepsis patients, like the workshop mentioned above, and reducing long term sepsis sequelae require more attention.

Therefore I'd like to call for more expertise and education on the hidden impairments of sepsis and to provide patients with more specific recovery tools, thus preventing readmissions and help them to improve their quality of life; the life that was so hard-won. ■

References

For full references, please email editorial@icumanagement.org or visit https://iii.hm/de0

HELLENIC SOCIETY OF INFECTIONS IN CRITICALLY ILL PATIENTS • H.E.L.I.A.S. • 2015 •

UNIVERSITY GENERAL HOSPITAL, ATHENS
ATTIKON

ATHENA 2017
International Conference

APPROACHING THE SEVERELY INFECTED PATIENT

28-30 NOVEMBER 2017
DIVANI CARAVEL HOTEL - ATHENS GREECE

www.ATHENAconference.com

Secretariat-Informations:
KEGM Tourist & Congress Operations SA
Congress World
27, Michalakopoulou Ave., 11528 Athens Greece
Tel.(0030)2107210001,2107210052, Fax.(0030)2107210051
info@congressworld.gr, reception@congressworld.gr

Franceso Mojoli
Consultant intensivist
Anaesthesia and Intensive Care
Fondazione IRCCS Policlinico
S. Matteo
Pavia, Italy

Department of clinical-surgical,
diagnostic and paediatric sciences
University of Pavia
Pavia, Italy

francesco.mojoli@unipv.it

Silvia Mongodi
Consultant intensivist
Anaesthesia and Intensive Care
Fondazione IRCCS Policlinico
S. Matteo
Pavia, Italy

silvia.mongodi@libero.it

Ultrasound-guided mechanical ventilation

Point-of-care ultrasound (POCUS) is now a tool used worldwide, integrating clinical assessment of the critically ill. In this review, we focus on lung, diaphragm and cardiac ultrasound in the management of the mechanically ventilated patient. Ultrasound provides useful information to assess and monitor lung aeration, to set mechanical ventilation and to early identify respiratory complications, such as pneumothorax, pneumonia and pleural effusion. Finally, we describe how to integrate ultrasound findings to manage weaning from mechanical ventilation.

In the last years, ultrasound (US) became an essential tool in the hands of the intensivist and is now recommended both for procedural guidance and diagnostic purposes. Point-of-care ultrasound (POCUS) is an immediately available and repeatable, non-irradiating bedside tool integrating the clinical examination.

While echocardiography has a longer history in critical care and remains the most frequently used technique (Zieleskiewicz et al. 2015), recent years were characterised by a growing interest in the fields of lung and diaphragm US. The evolution and combination of these three US techniques may integrate the classical approach to mechanically ventilated patients, both for monitoring (Bouhemad et al. 2015) and diagnostic purposes (Riviello et al. 2016), finally contributing to the titration of mechanical ventilation (Luecke et al. 2012) and to the management of respiratory disease.

Lung aeration assessment

Lung ultrasound (LUS) semiotics is mainly composed by artefacts. A normally aerated lung is characterised by A lines: horizontal reverberation artefacts beneath the pleural line. When the ratio between air and tissue is impaired, vertical artefacts called B lines appear: their number and coalescence are proportional to lung density (Soldati et al. 2012) and loss of aeration (Via et al. 2010). Therefore a number of LUS scores based on number and type of visualised artefacts have been proposed in the last years to allow semi-quantification of lung aeration. The most frequently used score in the intensive care unit (ICU) distinguishes 6 areas per hemithorax: sternum, anterior and posterior axillary lines identify anterior, lateral and posterior regions, each divided in superior and inferior fields (Bouhemad et al. 2010; Soummer et al. 2012). In each area, a central intercostal space is examined and a score attributed according to the number and coalescence of B lines (**Figure 1**): A lines or ≤2 B lines correspond to normal aeration (score 0); ≥3 well-spaced B lines correspond to moderate loss of aeration (score 1); coalescent B lines correspond to severe loss of aeration (score 2); the presence of tissue-like pattern corresponds to consolidation and therefore to complete loss of aeration (score 3). The LUS score corresponds to the sum of each area's score and ranges from 0 (all areas are well aerated) to 36 (all areas are consolidated); it showed a good correlation with extravascular lung water (Zhao et al. 2015) and computed tomography (CT) scan (Mongodi et al. 2014). It was successfully used in weaning from mechanical ventilation (Soummer et al. 2012) and guidance to fluid resuscitation (Caltabeloti et al. 2014). A re-aeration score, based on the same patterns, may also be computed and was successfully applied to assess positive end-expiratory pressure (PEEP)-induced recruitment (Bouhemad et al. 2011) and recovery after one week of antibiotic therapy in patients affected by ventilator-associated pneumonia (Bouhemad et al. 2010).

A recent study (Mongodi et al. 2017a) highlighted limitations of this score: it's in fact suitable for homogeneous loss of aeration, when coalescence is generated by an increased number of B-lines. However, it may tend to overestimate loss of aeration when the lung pathology is non-homogeneous, such as in acute respiratory distress syndrome (ARDS), pneumonia and trauma, where focal coalescence and subpleural consolidations are frequent. To overcome this limitation, it was proposed to assign a LUS score 1 or 2 (moderate or severe loss of aeration, respectively) according to the percentage of pleura (≤ or >50%) interested by B-lines or sub-pleural consolidations (Mongodi et al. 2017a). Moreover, guidelines suggest using a longitudinal scan in order to visualise the pleura between the ribs' shadow; however, a transversal approach aligned with the intercostal space allows visualisation of significantly wider pleura and higher number of artefacts (Mongodi et al. 2017a). Automated systems of semi-quantification are also currently under evaluation (Corradi et al. 2016).

Recruitment manoeuvre, PEEP setting and prone position

A direct monitoring of re-aeration during recruitment manoeuvre can be performed

bedside by LUS (Nguyen et al, 2016): when a consolidated lung is successfully re-aerated by the manoeuvre, a real-time switch from a tissue-like pattern to an artefact pattern can be visualised, corresponding to the increase of air within the lung area (**Figure 2**).

A single group studied the assessment of PEEP-induced recruitment by LUS: when compared to pressure volume (PV) curve, a re-aeration score > 8 corresponded to a gain of 600 ml (Bouhemad et al. 2011). Moreover, the distribution of US artefacts and therefore of loss of aeration helps in predicting recruitment: as already assessed by CT (Constantin et al. 2010), patients with focal loss of aeration, thus with normal anterior fields, are classified as non-recruiter; high PEEP and recruitment manoeuvres are here contraindicated. On the other hand, patients with diffuse loss of aeration (i.e. affecting also anterior fields) may positively respond to recruitment and an US-monitored PEEP trial is recommended.

When patients are classified as non-responder to PEEP, they may positively respond to prone position (Prat et al. 2015). Patients with focal loss of aeration, compared with those with a diffuse disease, showed in fact a greater improvement of aeration in posterior lung areas during pronation (Haddam et al. 2016). A significant re-aeration of posterior fields during the first cycle of pronation identified "long-term" responders to prone position, defined by a P/F (pO_2/FIO_2) ratio >300 mmHg after 7 days of 6-hour prone position twice daily (Wang et al. 2016). In this experience, re-aeration assessed by US was associated with the decrease of dead space and also with better outcome, a finding consistent with previous observations (Gattinoni et al. 2003).

Heart-lung interaction

High-pressure mechanical ventilation has some drawbacks: not only does it expose to barotrauma and higher risk of complications, but it may also have a negative impact on gas exchange and haemodynamics due to lung over-distention and right ventricle (RV) impairment (Repessé et al. 2015).

Overdistention mainly affects anterior fields, impairing both alveolar ventilation and vascularisation, favouring perfusion of non-aerated regions (i.e. shunt) thus worsening respiratory acidosis and hypoxaemia. Over-distention cannot be formally measured by US; however, a reduction of physiological pleural sliding in anterior regions may be observed while increasing airway pressure (Markota et al. 2016; Pesenti et al. 2016).

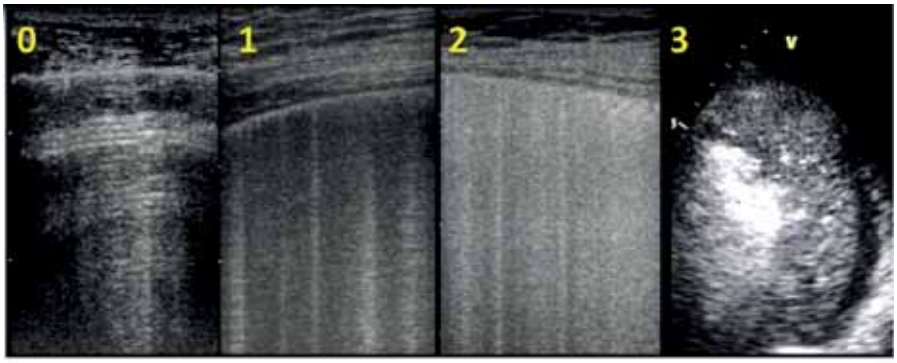


Figure 1. Progressive loss of aeration and corresponding lung ultrasound score from normal (left) to complete loss of aeration (right) – transversal view, linear probe (0-2) and phased-array probe (3).

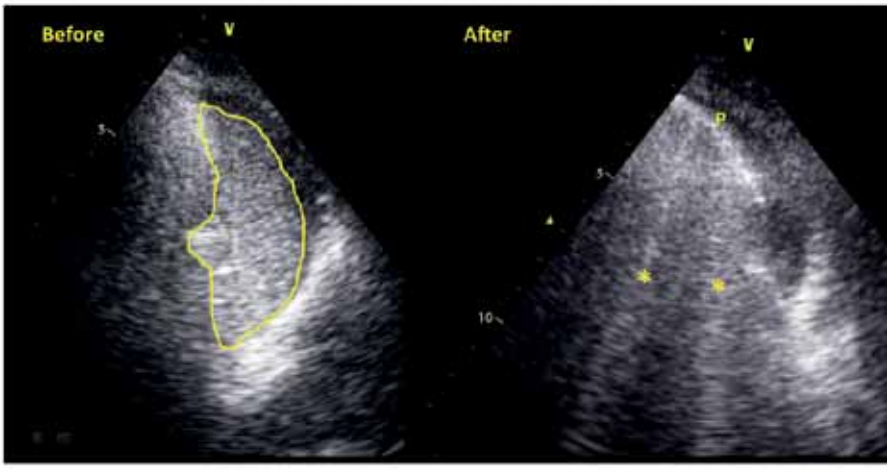


Figure 2. Before: tissue-like pattern with no air bronchogram corresponding to complete loss of aeration and no patent airways. After: reaeration after fiberbronchoscopy removing secretions and recruitment manoeuvre, with switch to an artefact pattern where the pleural line (P) and B lines (*) are visible – transversal view with phased array probe.

Moreover, an increase of airway pressure may substantially increase RV afterload. This may complicate a scenario already characterised by pulmonary vasoconstriction induced by hypoxaemia and respiratory acidosis eventually leading to a significant worsening of haemodynamics (Mongodi et al. 2017b). Incidence of acute cor pulmonale (ACP) in ARDS ranges from 14 to 50% (Repessé et al. 2015; Mekontso Dessap et al. 2016).

ACP may be detected by transthoracic echocardiography (TTE) as an enlarged RV (right to left ventricle end-diastolic area ratio >0.6, **Figure 3**) and a paradoxical septal motion (Repessé et al. 2015).

Pulmonary hypertension secondary to increased airway pressure may lead to a right-to-left shunt through a previously silent patent foramen ovale (PFO), significantly worsening hypoxaemia (Mekontso Dessap et al. 2010; Mongodi et al. 2017c). The gold standard for patent PFO diagnosis is transoesophageal echocardiography; however, TTE examination with bubble test presents high specificity and reliably identifies significant shunts (Mojadidi et al. 2014). Only rare cases of PFO paradoxical response to PEEP are reported in the literature (Tavazzi et al. 2016).

Prone position may help in unloading the RV by correcting the factors inducing pulmonary vasoconstriction (i.e. hypoxaemia, hypercarbia) with no increase of airway pressure (Vieillard-Baron et al. 2007).

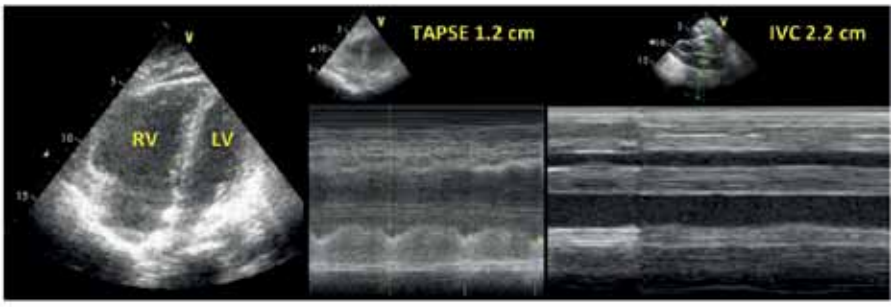


Figure 3. From left to right: transthoracic apical four chamber view showing a failing right ventricle (RV), which appears larger than the left ventricle (LV); the tricuspid annular plane systolic excursion (TAPSE), a marker of RV contractility, is severely reduced (1.2 cm); inferior vena cava (IVC) is distended and fixed (diameter 2.2cm), with no significant variation in m-mode during tidal ventilation, corresponding to increased RV afterload.

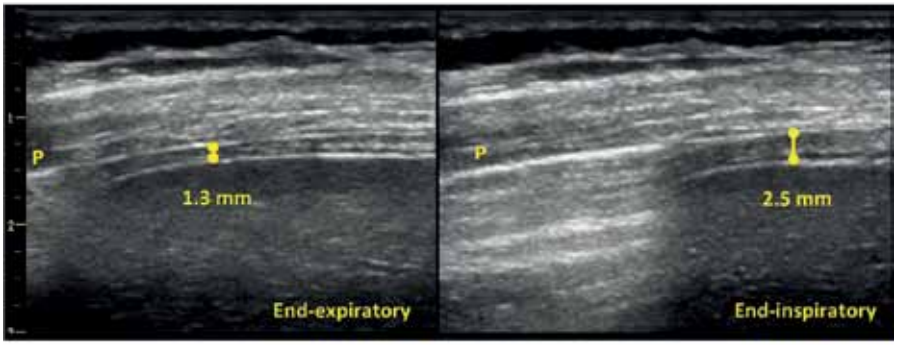


Figure 4. Diaphragm visualisation at the zone of apposition by linear probe. A significant variation of the muscle thickness is measured from end-expiration (1.3 mm) to end-inspiration (2.5 mm) during a deep breath, corresponding to normal contractility (thickening fraction 0.92). P: Pleural line.

Therefore, a combination of lung and heart US findings may help in setting the best PEEP level, considering both lung aeration and haemodynamic impact.

Respiratory complications in mechanically ventilated patients

Pneumothorax

Pneumothorax can be a consequence of barotrauma, mainly when lung compliance is reduced. LUS is accurate in the diagnosis of pneumothorax (Lichtenstein et al. 2000) and is superior to supine anterior chest x-ray (Blaivas et al. 2005). If a pneumothorax is suspected, LUS should be performed following a simple algorithm (Mongodi et al. 2016a). The presence of real images (consolidation, effusion), of any pleural movement (sliding, lung pulse) or artefacts deriving from the visceral pleura (B-lines) rules out pneumothorax with 100% negative predictive value. If a static A pattern is visualised, a lung point must be searched moving the probe laterally and inferiorly: the lung point corresponds to the site where the collapsed lung goes back in touch with the parietal pleura and rules in pneumothorax with 100% positive predictive value. If no lung point is identified, the positive predictive value of a static A pattern alone ranges from 55 to 98%, depending on the clinical context; for example, if the lung is completely collapsed, no lung point can be visualised.

Although the exact size of the pneumothorax cannot be measured by US, an estimation of the percentage of collapsed lung may be suggested by the location of the lung point on the chest wall: if below the mid-axillary line in supine patients, it corresponds to lung collapse >15% with sensitivity 83.3% and specificity 82.4% when compared with CT scan (Volpicelli et al. 2014).

Depending on the expected percentage of lung collapse and on the patient's clinical stability, LUS may guide the intensivist in the decision to drain the air collection, while allowing visualisation of parietal vessels to be avoided (Mongodi et al. 2016a).

Pleural effusion

Effusions are visualised by US as anechoic areas between the parietal and visceral pleura. US also provides morphologic assessment, suggesting the possible aetiology of fluid collection, and allows estimation of the amount of fluid that can be drained (Balik et al. 2006). Finally, US is a reliable guide to thoracentesis (Lichtenstein et al. 1999).

Consolidations

LUS accurately identifies lung consolidation and, being dynamic, is a useful tool to distinguish consolidation aetiologies by looking at air bronchograms (Berlet et al. 2015).

Air bronchogram is visualised within a consolidation as white hyperechoic spots due to air trapped inside the bronchi. When it moves during tidal ventilation—the so-called dynamic air bronchogram—the airway is patent but alveoli are not: therefore ventilator-associated pneumonia can be suspected.

While consolidation alone is poorly specific (Zagli et al. 2014), two ultrasonographic signs of VAP have been identified: subpleural consolidations and dynamic linear/arborescent air bronchogram. These signs were combined with a clinical parameter (purulent secretions) into a simple score (Ventilator-associated Pneumonia Lung Ultrasound Score), which performed better than the classical Clinical Pulmonary Infection Score, even when combined to direct exam of tracheal aspirate (Mongodi et al. 2016b). Moreover, LUS allows monitoring of antibiotic effects: the computation of the LUS re-aeration score after one week of antibiotic treatment distinguishes responders from non-responders, eventually redirecting the therapeutic approach (Bouhemad et al. 2010).

On the other hand, when the bronchogram is absent or static, i.e. not moving during tidal ventilation, the consolidation presents airway obstruction. In fact, air cannot enter the bronchi during ventilation and the mechanism leading to loss of aeration might be reabsorption atelectasis. Fiberbronchoscopy is here indicated to clear the bronchi and restore normal airflow and lung aeration (**Figure 2**).

Finally, the impact on gas exchanges of a given consolidation depends on perfusion of the non-aerated tissue, i.e. intrapulmonary

shunt; to grossly assess shunt, blood flow can be visualised by applying colour Doppler on the tissue-like pattern (Mongodi et al. 2016c).

Diaphragmatic dysfunction

US can assess both diaphragm morphology and function by measuring its thickness, excursion and thickening fraction. The muscle thickness is a static measurement obtained by examining the diaphragm with a linear probe at the zone of apposition to the thoracic wall, where the diaphragm is visualised as a double binary structure parallel to the probe. It's a very reproducible measure (Goligher et al. 2015a), more easily obtained on the right side, and provides significant information about the muscle status. It has been shown that diaphragm thickness progressively declines during mechanical ventilation, being a marker of the increasing atrophy of the muscle, especially in cases of controlled mechanical ventilation or high-level assisted mechanical ventilation (Schepens et al. 2015; Hudson et al. 2012). Diaphragm excursion consists in muscle dome caudal displacement during inspiration (Kim et al. 2011), and can be quantified by m-mode technique with a phased-array probe. This measurement presents two main limitations: first, m-mode may not be aligned with the course of the diaphragm, thus leading to underestimation of the excursion. This can be avoided by the use of the anatomical m-mode (Pasero et al. 2015). Second, diaphragm excursion in ventilated patients is affected by the pressure support delivered by the ventilator; active and passive displacement cannot be distinguished. Instead, active contractility can be detected as an increase in muscle thickness during respiratory efforts (**Figure 4**), and the diaphragm thickening ratio, i.e. (thickness at end-inspiration – thickness at end-expiration) / thickness at end-expiration, can be used as a measure of muscle activity. Ideally, to avoid both disuse atrophy and stress injury of the diaphragm, during assisted ventilation the level of support could be titrated according to diaphragm activity assessed by US. (Goligher et al. 2015b).

Weaning from mechanical ventilation

The weaning process from mechanical ventilation covers up to 40-50% of total mechanical ventilation time (McConville and Kress 2012). Weaning failure ranges from 25 to 61% (Esteban et al. 1999), depending on the clinical context; multiple physiopathological mechanisms may be involved, therefore weaning process remains a significant challenge for the intensivist. Three of the main mechanisms leading to weaning failure can be assessed by US: cardiac dysfunction, lung derecruitment and diaphragm dysfunction.

While no impact of systolic parameters has been found, diastolic assessment by transmitralic pattern and tissue Doppler of mitral annulus can identify the failing patient with moderate sensitivity and high specificity (Moschietto et al. 2012). The assessment of lung aeration score at the end of a spontaneous breathing trial predicts extubation failure with 0.86 area under curve (AUC) (Soummer et al. 2012). Finally, respiratory muscles dysfunction as assessed by diaphragm US during a spontaneous breathing trial or low-pressure support ventilation is associated with weaning failure. (Kim et al. 2012; Spadaro et al. 2016; Blumhof et al. 2016).

A combined US approach assessing lung, heart and diaphragm has been suggested, not only for early identification of the failing patient but also for a better understanding of the underlying mechanism of failure, thus guiding therapeutic management to improve weaning success rate (Mongodi et al. 2013; Mayo et al. 2016).

Conclusions

Lung, diaphragm and cardiac US provide significant information to improve the management of the critical patient under mechanical ventilation, from the initial assessment, through the ventilation setting and its complication diagnosis, until the weaning process. ■

Conflict of interest

Francesco Mojoli received fees for lectures from GE healthcare and for lectures and consultancy from Hamilton Medical. Silvia Mongodi declares that she has no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome
ICU intensive care unit
LUS lung ultrasound
PFO patent foramen ovale
PEEP positive end-expiratory pressure
RV right ventricle
US ultrasound
VAP ventilator-associated pnuemonia
RV right ventricle
TTE transthoracic echocardiography

References

Balik M, Plasil P, Waldauf P et al. (2006) Ultrasound estimation of volume of pleural fluid in mechanically ventilated patients. Intensive Care Med, 32(2): 318.

Berlet T, Etter R, Fehr T et al. (2015) Sonographic patterns of lung consolidation in mechanically ventilated patients with and without ventilator-associated pneumonia: a prospective cohort study. J Crit Care, 30(2): 327-33.

Blaivas M, Lyon M, Duggal S (2005) A prospective comparison of supine chest radiography and bedside ultrasound for the diagnosis of traumatic pneumothorax. Acad Emerg Med, 9: 844-9.

Blumhof S, Wheeler D, Thomas K et al. (2016) Change in diaphragmatic thickness during the respiratory cycle predicts extubation success at various levels of pressure support ventilation. Lung, 194(4): 519-25.

Bouhemad B, Liu Z, Arbelot C et al. (2010) Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. Crit Care Med, 38(1): 84-92.

Bouhemad B, Brisson H, Le-Guen M et al. (2011) Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med, 183(3): 341-7.

Bouhemad B, Mongodi S, Via, G et al. (2015) Ultrasound for "lung monitoring" of ventilated patients. Anesthesiology, 122: 437-47.

Caltabeloti F, Monsel A, Arbelot C et al. (2014) Early fluid loading in acute respiratory distress syndrome with septic shock deteriorates lung aeration without impairing arterial oxygenation: a lung ultrasound observational study. Crit Care, 18(3): R91.

Constantin JM, Futier E, Cherprenet AL et al. (2010) A recruitment maneuver increases oxygenation after intubation of hypoxemic intensive care unit patients: a randomized controlled study. Crit Care, 14(2): R76.

Corradi F, Brusasco C, Vezzani A et al. (2016) Computer-aided quantitative ultrasonography for detection of pulmonary edema in mechanically ventilated cardiac surgery patients. Chest, 150(3): 640-51.

Esteban A, Alía I, Tobin MJ et al. (1999) Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med, 159(2): 512-8.

Gattinoni L, Vagginelli F, Carlesso E et al. (2003) Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med, 31(12): 2727-33.

Goligher EC, Laghi F, Detsky ME et al. (2015a) Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med, 41(4): 642-9.

Goligher EC, Fan E, Herridge MS et al. (2015b) Evolution of diaphragm thickness during mechanical ventilation. impact of inspiratory effort. Am J Respir Crit Care Med, 192(9): 1080-8.

Haddam M, Zieleskiewicz L, Perbet S et al. (2016) Lung ultrasonography for assessment of oxygenation response to prone position ventilation in ARDS. Intensive Care Med, 42(10): 1546-56.

Hudson MB, Smuder AJ, Nelson WB et al. (2012) Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. Crit Care Med, 40(4): 1254-60.

For full references, please email editorial@icu management.org or visit https://iii.hm/de6

Christiaan Boerma
Senior consultant ICU
Department of Intensive Care
Medical Centre Leeuwarden
Leeuwarden, the Netherlands

e.boerma@chello.nl

Haemodynamic monitoring

Stuff we never talk about

In order to make haemodynamic monitoring clinically successful it seems mandatory to have a comprehensive view on the incorporation of the measured variables in a team-adapted strategy.

Over the last decades the evolution of haemodynamic monitoring in critically ill patients has not been unequivocal. On the one hand it may be argued that haemodynamic monitoring is an essential part of intensive care medicine. Analogous to mechanical ventilation, patients are specifically referred to the intensive care unit (ICU) for (better) haemodynamic monitoring. As such, haemodynamic monitoring partly defines the necessity for the existence of ICUs. This perceived importance of haemodynamic monitoring has fuelled successful progress in this field. Over the years the stage transformed from the ability to measure blood pressure and the subjective assessment of peripheral circulation (Joly and Weil 1969), to (non) invasive measurement of cardiac output (Swan and Ganz 1975), regional circulation (Fiddian-Green and Baker 1987) and even microvascular blood flow (De Backer et al. 2002). Simultaneously, static measurements were replaced by dynamic challenges (Michard and Teboul 2002) to test the physiological reserve of individual patients. And we learned to refrain from our intrinsic drive to correct the measured values under all circumstances to normal or even supra-normal (Gattinoni et al. 1995). On the other hand large series of randomised controlled trials (RCTs) failed to associate haemodynamic monitoring with improved outcome in a large variety of devices and variables (Harvey et al. 2005; ProCESS Investigators et al. 2014).

This apparent controversy may be explained by many reasons. Selection of patients, alternative strategies in the control group, inadequate signification of obtained variables, such as the classical misinterpretation of central venous pressure for preload of the right ventricle (Kumar et al. 2004), and potential adverse effects of intensified treatment may all have played a role. But one thing these RCTs all have in common is the absence of integration of the obtained variables into the diagnostic and therapeutic process. The way doctors deal with (extra) data remains a black box (**Figure 1**). In general a device/variable is compared with no, or a different device/variable. Potential consequences for changes in the haemodynamic strategies are left out of the equation. In this article we aim to address a series of issues that may appear to be crucial to an effective introduction of a new haemodynamic monitoring device/variable, but are usually not extensively addressed in the literature. Awareness of the discussed topics may help ICU decision makers to improve implementation strategies related to haemodynamic monitoring.

Pre-test likelihood

Ultimately all haemodynamic measurements will become a trigger to change or to persist in the existing haemodynamic strategy, i.e. to give fluids, maintain the dose of norepinephrine, stop dobutamine, etc. Cut-off values for such dichotomous decisions (yes/no) may be generated by static values (i.e. transfusion trigger), by trends of values over time (i.e. a decrease in blood pressure in comparison to baseline), or after specific challenges (i.e. fluid challenges). In this respect general knowledge on test results applies to haemodynamic monitoring as well. Apart from specificity and sensitivity, pre-test likelihood is of utmost importance when it comes to correct interpretation of test results. Using a test with a sensitivity of 100% and a specificity of 99.9% in a population of 10 million people for a disease with an incidence of 1 per million will inevitably lead to 10,000 false-negative test results. Improvement of the test quality is unlikely to resolve the problem, but the application of the test to the above situation is simply inadequate, creating chaos instead of solutions. Translating this to haemodynamic monitoring implies the need for a strategy to identify subgroups of patients with a considerable likelihood to have underlying haemodynamic abnormalities rather than measure a variable simply because the instrument is available. It seems key to have a predefined plan, supported by the entire ICU team, to define which patients are eligible for a specific type of haemodynamic monitoring. And it seems equally important to define which patients should *not* be subject to this specific type of haemodynamic monitoring.

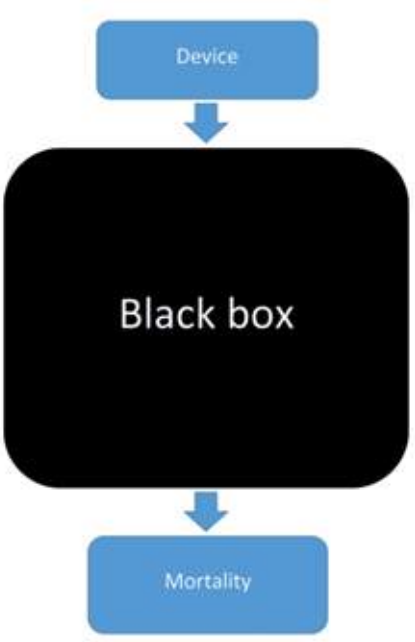


Figure 1. Classical test setting to assess the effect of haemodynamic monitoring

Timing

Initiation. The moment of initiation to set up a haemodynamic monitoring device is another factor contributing to its potential success or failure. It is not uncommon to postpone the use of haemodynamic monitoring until the ICU team has run out of the usual options, most commonly the administration of fluids and norepinephrine. Although it does not seem unreasonable to try conventional therapeutic strategies before introduction of potentially dangerous invasive procedures, this strategy carries two potential risks. Haemodynamic monitoring may be helpful to diagnose underlying mechanisms for circulatory failure, for example to answer the question: Is it really cardiogenic shock, or is septic shock more likely? Knowledge about the type of shock may not only change the perspective on the haemodynamic strategy, but also on treatment of underlying causes. Delaying haemodynamic monitoring until after the initial treatment may result in non-specific data, blurring its original extremes. This phenomenon, generally referred to as regression to the mean (Morton and Torgerson 2003), is created by the fact that in critically ill patients haemodynamic monitoring only is started in those who survived the initial emergency (and treatment).

A second consequence of delaying haemodynamic monitoring is the reduction in power of its potential. In a classic RCT patients with adult respiratory distress syndrome (ARDS) were randomised for the use of a pulmonary artery catheter (PAC) (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network et al. 2006). In short there was no difference in mortality between groups. However, the average duration to insert the PAC was almost 2 days (> 40 hours). And by that time both groups received 4.9 litres of fluids. It is hard to imagine how any form of haemodynamic monitoring could still have a therapeutic advantage under those circumstances in ARDS patients. Even if the device could provide information that would lead to the immediate cessation of additional fluid administration, the damage of fluid overload has already taken place. Correction by diuretics is not always possible and is not equal to prevention.

Since haemodynamic monitoring is not feasible under all conditions it remains reasonable to treat first that kills first. But after initial stabilisation (hours) it seems eminently reasonable to start haemodynamic monitoring as soon as possible, and not to postpone (days).

Sampling rate. Even a high-precision monitoring device may miss valuable information if the sample rate is inadequate for the situation at hand. During the construction of a subway system beneath the swampy soil of Amsterdam, engineers installed a precision monitoring instrument with mirrors and lasers, attached to the walls of historical buildings, in order to detect the slightest movement (mm!). Nevertheless in 2008 a complete block of buildings sagged suddenly, to the extent that all doors jammed and occupants had to be evacuated through the windows. Emergency constructions were needed to prevent total collapse. Was the monitoring system inadequate? No. The event

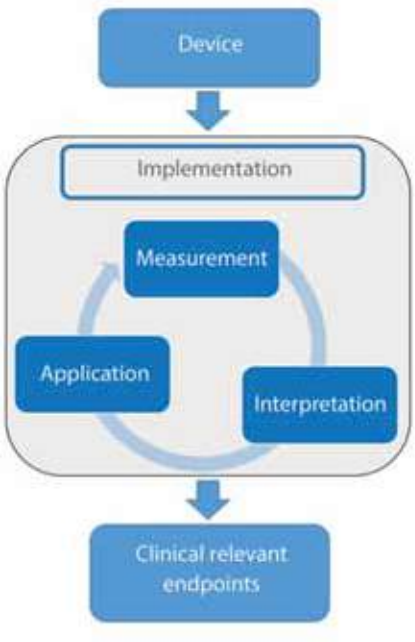


Figure 2. Integrative approach to implement haemodynamic monitoring successfully

simply took place within minutes, whereas measurements were performed every two hours. This example refers to the Nyquist-Shannon theorem, originating from the early days of the telephone industry, in which analogue-to-digital signal conversion appeared to be a challenge. It states that in order to prevent distortion, a sample rate twice as high as the frequency of changes in the original signal is needed (Nyquist 1928). How should we translate this into haemodynamic monitoring? Since haemodynamic changes may take place within minutes, especially during interventions, monitoring on a near-continuous basis is needed to prevent unintentional drop-out of vital information. Measurements of cardiac output once per shift or even once per hour are simply inadequate. And what is true for the measurements themselves is also true for the registration of variables. Patient data management systems (PDMS) are needed to register changes in haemodynamic variables on a near-continuous basis. And they should preferably provide support in analysing trends not immediately clear to the human eye.

Human behaviour

One of the most undervalued influencing factors in the success or failure of haemodynamic monitoring is human behaviour. The vast majority of papers in this field deal with accuracy and precision. Implementation into clinical practice is generally left 'to the discretion of the attending physician'. However, the recent FENICE study urges us to reconsider such (absence of) strategy (Cecconi et al. 2015). In centres all over Europe doctors not only defined partially wrongful endpoints of fluid resuscitation for themselves. The most shocking part of the results is the fact that in general the test result did not influence their decision to continue fluid administration. In other words patients received equal amounts of fluids, irrespective of a positive, negative or indifferent result. Under such conditions it is impossible to make a difference with haemodynamic monitoring. Recently we had similar experiences. Despite a detailed training programme the introduction of passive leg raising (PLR) in patients with septic shock did not result in a difference in median fluid balance 48 hours after ICU admission (Rameau et al. 2017). Re-evaluation with all medical and paramedical members of the ICU team revealed that compliance to test results was extremely low. During a plenary discussion representatives of all disciplines (including staff!) 'confessed' that they trusted their own gut feeling more than the test result. Subsequently the team decided in favour of an additional trial period, in which adherence to the test result of PLR was now key. After 'correction' of the behavioural issue the trial was now positive, with a significant reduction in the use of fluids.

These examples extend beyond a common implementation plan. It involves the fundamental insight that medical personnel are not only driven by reason, but by emotions and habits too. Herbert Simon introduced the Nobel prize-winning idea of heuristics (Simon 1983). He demonstrated that humans operate in what he called bounded rationality, referring to the situation where people seek solutions that are 'good enough' for their purposes, but could be optimised. In effect, a cognitively difficult problem is dealt with by answering a rather simpler problem, without being aware of this happening. Such an approach helps us to solve complex problems, that is to make decisions, even if we do not understand the full picture. It is a form of mental shortcut. The downside of such an approach is an unwitting rejection of new concepts and ideas, as long as we see fit to use the old ones. The unaware character of such resilience to behavioural changes with respect to healthcare professionals has profound consequences for clinical practice in general, and for the application of haemodynamic monitoring in particular. It implies that introduction of new devices and strategies is not restricted to theoretical and practical issues, such as education and training. It means that we have to monitor this process carefully, since even simple and cheap interventions, based on solid scientific principles, may not be associated with results according to our expectations (Rameau et al. 2017). Bridging this knowledge-to-care gap is one of the challenges (Cochrane et al. 2007) needed to convert a 'simple' haemodynamic measurement into a powerful clinical tool that has impact on morbidity and mortality of critically ill patients.

Conclusions

In hindsight it is not surprising that as of now there is an absence of relationship between haemodynamic monitoring and improved outcome. We have learned from the past that the success of haemodynamic monitoring depends on many aspects beyond the technical issues of accuracy and precision. Others already alluded to the idea of a chain of events needed for a positive result: correct measurement, correct interpretation and correct application (Vincent et al. 2008). This chain may become more detailed and even longer, as we better understand technical and behavioural issues of this previously black box (*Figure 2*). All parts of the chain need to be in place as a prerequisite for success. ■

Conflict of interest

Christiaan Boerma declares that he has no conflict of interest.

Abbreviations

ICU intensive care unit
PAC pulmonary artery catheter
PDMS patient data management system
PLR passive leg raising
RCT randomised controlled trial

References

For full references, please email editorial@icu management.org or visit https://iii.hm/de8

Animal-assisted activity in the intensive care unit

Outlines some basic considerations for ICU providers interested in incorporating animals into care programmes.

Megan M. Hosey*
Assistant Professor and Clinical Psychologist
Department of Physical Medicine & Rehabilitation
Division of Rehabilitation Psychology and Neuropsychology

Outcomes After Critical Illness (OACIS) Group

Johns Hopkins School of Medicine, Baltimore, MD, USA

mhosey@jhmi.edu

@DrMeganHoseyPhD

Janice J. Jaskulski
Physical Medicine and Rehabilitation Team Lead, Psychiatry
Animal Assisted Activity/Therapy Coordinator
Johns Hopkins Hospital
Baltimore, MD, USA

jjaskul@jhmi.edu

Earl C. Mantheiy
Senior Clinical Program Coordinator
Critical Care Physical Medicine and Rehabilitation Program (CCPM&R)
Johns Hopkins School of Medicine, Baltimore, MD, USA

Dex@jhu.edu

Sapna R. Kudchadkar
Director, Johns Hopkins PICU Clinical Research Program
Assistant Professor, Department of Anesthesiology and Critical Care Medicine
Johns Hopkins School of Medicine, Baltimore, MD, USA

sapna@jhmi.edu

@SapnaKmd

Stephen T. Wegener
Professor, Department Physical Medicine and Rehabilitation
Director, Division of Rehabilitation Psychology and Neuropsychology
Johns Hopkins School of Medicine, Baltimore, MD, USA

swegener@jhmi.edu

Dale M. Needham
Professor, Outcomes After Critical Illness & Surgery (OACIS) Group, Division of Pulmonary & Critical Care Medicine and Department of Physical Medicine & Rehabilitation

Medical Director, Critical Care Physical Medicine & Rehabilitation Program

Johns Hopkins School of Medicine, Baltimore, MD, USA

Dale.needham@jhmi.edu

@DrDaleNeedham

Animals are being introduced into hospital settings in ever-increasing numbers. Emerging literature suggests that incorporating trained animals to assist with medical care and rehabilitation therapies can promote patient engagement, reduce emotional distress and relieve some aspects of physiologic burden. Below, we outline some basic considerations for ICU providers interested in incorporating animals into care programmes.

Why include animals in the ICU?

An increasing number of patients are surviving critical illness, resulting in increased attention to understanding patients' experience while in the intensive care unit (ICU). As a result, new insights have been gained regarding enhancing the ICU environment, including "humanizing"' the ICU (Brown et al. 2016). In examining ways to improve the patient experience, some healthcare facilities integrate animal therapy as a means to support patients' mood (Bernabei et al. 2013; Hoffmann et al. 2009), increase engagement in rehabilitation therapies (Muñoz Lasa et al. 2011) and reduce aspects of physiologic symptoms (e.g., pain) (Halm 2008). Animal therapy has been used in a wide range of patient groups ranging from paediatrics to geriatrics. Publications focused on animals in the ICU setting are scant, with anecdotes suggesting that animal presence in the ICU is beneficial to patients (Lee and Higgins 2010).

What are animal-assisted activity and animal-assisted therapy?

When animals and their handlers (therapy animal teams) are incorporated into care settings, they may serve in several roles, with specified terminology used to describe each role. First, animal-assisted activity (AAA) is a term referring to the use of trained animals for the therapeutic, motivational or educational benefit of patients (Delta Society 2006) (**Table 1, Figure 1**). Animal-assisted therapy (AAT) refers to the practice of rehabilitation therapists working with specialty trained animals to facilitate specific, measurable goals for individual patients for whom there is documentation of progress (Kruger et al. 2006). Use of the term "pet therapy" may be best reserved for instances when patients' own pets are involved for purposes of emotional support. Although dogs are most commonly employed in hospital settings, other animals used in AAA/AAT have included dolphins, cows, birds, horses, fish, llamas and cats (Morrison 2007).

The above terms should not be confused with a visit from a "service animal," "emotional support animal," or the patient's pet (Brennan 2014; **Table 1**). A visit by such animals needs to be a well-considered decision by the clinical team, with input from legal and infection control services within the facility and review of any facility-specific policy.

When should animals be incorporated into a treatment plan?

Literature regarding the benefits of AAA/AAT provides some guidance about which critically ill patients may benefit most. Several studies have documented the effectiveness of AAA/AAT in patients with mental health symptoms, including symptoms of depression, anxiety and loneliness (Wu et al. 2002; Banks and Banks 2002). For example, dog visitation in a paediatric cardiac inpatient setting was associated with both children and parents reporting reduced levels of stress and higher levels of positive affect after a 10-20 minute visit. Similarly, AAA/AAT has increased patient satisfaction among trauma survivors (Stevens et al. 2017). Consequently, ICU clinicians may consider prioritising

AAA/AAT to patients with hospital-related demoralisation and high anxiety.

A favourite patient experience at our institution is that of a paediatric ICU patient, receiving extracorporeal support, with a length of stay >600 days. She missed her home, a farm several hours from the hospital. In particular, she missed her cow, Pantene. Consequently, family members and ICU staff coordinated an effort to bring her cow to the hospital courtyard so that she could pet her and have a connection to home. The joy of that moment, experienced by that patient (and staff), has a lasting positive effect.

> "potential to reduce stress and suffering in ICU patients"

Furthermore, AAT may increase patient engagement and improve performance during rehabilitation sessions (Muñoz Lasa et al. 2011). Specifically, patients with known difficulties participating in rehabilitation and mobility interventions may be good candidates for AAT. Numerous studies report an association between AAA/AAT and improved symptoms including pain (Halm 2008, Morrison 2007), making ICU patients with persistently high levels of pain potential candidates. Finally, AAA/AAT has been associated with improved learning among people with acquired cognitive disabilities (Bernabei et al. 2013) which might be beneficial in the ICU setting given high rates of cognitive changes, such as delirium.

Are there risks or contraindications in AAA/AAT?

There are some risks and contraindications to AAA/AAT (Brodie et al. 2002). Some patients may be allergic to pet dander or averse to animal visits. Asking patients and families about their level of interest is important to ensure that only those patients who welcome AAA/AAT receive visits. Institutions remain vigilant to the risk of infectious diseases. Working with institutional infection control programmes will help ensure that both patients and animals stay healthy. Such programmes can guide teams toward preventing zoonotic infection (i.e., transmitting disease from animal to human), reducing risk of fomite contamination with an animal carrying a pathogen from one patient to another patient on fur, leash or vest. In our institution, these issues have resulted in guidelines that include bathing and grooming requirements for animals prior to coming to the hospital, as well as handwashing or sanitising before and after each patient visit. Moreover, dog licks are prohibited at our institution, as well as visits from animals on raw diets. For patients on contact precautions or isolation, infection control practitioners and the clinical team can make case-by-case decisions regarding the risks and benefits to the patient and therapy animal.

How can animal-assisted activity be built into an existing team?

When considering an AAA programme, an integral first step is to find a champion who is passionate about creating this culture change. This person is typically a key stakeholder, consistently present in the organisation,

Table 1. Common terminology in animal-assisted therapy

Term	Definition
Animal-Assisted Activity	"Use of a trained animal for the therapeutic, motivational, or educational benefit of patients"
Animal-Assisted Therapy	"Use of a trained animal by health professionals to facilitate specific, measurable goals for individual patients for whom there is a documentation of progress"
Pet Therapy	Pet therapy is an older, generic term that may be used to designate a visit from a patient's own, typically untrained, pet. This terminology is being used with less frequency over time.
Emotional Support Animal	"Use of a non-trained animal to provide companionship, relieve loneliness, and sometimes help with depression, anxiety, and specific phobias in an individual."
Service Animal	"Use of a trained animal to assist an individual in managing activities of daily living or monitoring health status."

Definitions adapted from the american disabilities act national network

Figure 1. Patient receiving mechanical ventilation via an oral endotracheal tube sits at edge of bed to pet Tattoo, a therapy dog, in the medical intensive care unit at Johns Hopkins Hospital

who has access to institutional resources and ability to influence systemic change. Physicians, rehabilitation therapists, nurse educators and managers, and social workers are all potential champions. AAT programmes require rehabilitation therapist involvement as they utilise the therapy animal team as a modality for patient treatment.

Identify goals

A next important step is to identify the goals of the AAA/AAT programme. If these goals are well circumscribed, the likelihood that the programme (usually a scarce resource in early stages) will reach patients in a way that maximises benefits. Programmes that are implemented without clear patient and programme goals will have a more difficult time documenting and highlighting the improvement in patient-related outcomes.

Protocol/ policy

We also suggest partnering with other key stakeholders to build a protocol/policy that will serve to create a structure for the programme, limit risk to patients and animal therapy teams, and support ongoing programme evaluation. Important disciplines involved in protocol development include physical medicine and rehabilitation, nursing, infection control, risk management and volunteer services. A protocol/policy should include the following:

1. **Responsibility of all involved parties:** programme coordinator, animal team (handler), volunteer office, patient care team, infection control practitioner
2. **Procedure:** how and where animals can visit, how long animals can visit, policy for photos, structure of the animal visit, disclosure of potential risks to the patient and animal therapy team
3. **Reportable conditions and events:** animal bites or scratches, patient harm to animal or handler, zoonosis or transmission of organism to therapy animal, unexpected animal death
4. **Documentation of visits in the patient medical record and in the unit records:** when, what and who should record
5. **Programme evaluation:** ways to effectively measure the frequency and effectiveness of the visits

For assistance in building a protocol, some helpful resources include a set of guidelines for animal-assisted intervention to minimise spread of infectious disease (Lefebvre et al. 2008), references that enhance learning about standards of practice (e.g. Delta Society 2003), and guides that reinforce the definitions of AAA/AAT (e.g. Brennan 2014).

Resources

Once an AAA/AAT programme has a champion and identified goals, the next step is to find an organisation experienced in training therapy animal teams. Valuable resources that help with vetting and training of animal therapy teams include organisations such as Pet Partners, Inc. (petpartners.org), Therapy Dogs International, Inc., The American Kennel Club (akc.org/events/title-recognition-program/therapy) and Assistance Dogs International (assistancedogsinternational.org). Socialisation, obedience and temperament assessment are all components of the certification process. Reviewing these resources can help handlers and institutions find a training group that is local, experienced, and free from commercial bias.

Conclusion

Although limited, early evidence suggests that AAA/AAT is a therapeutic activity that has potential to reduce stress and suffering in ICU patients. Carefully matching well-trained animal teams to patients may result in reduced emotional stress, increased patient satisfaction, and ease of physiological burden. When an AAA/AAT programme has a passionate champion and a strong institutional protocol, it can maximise success and benefit. ■

Figure 2. Patient receiving extracorporeal membrane oxygenation (ECMO) and mechanical ventilation via a tracheostomy at the paediatric intensive care unit at Johns Hopkins Hospital stands with assistance of a walker to greet a cow from her family farm

Abbreviations

AAA animal-assisted activity
AAT animal-assisted-therapy
ICU intensive care unit

References

Banks MR, Banks WA (2002) The effects of animal-assisted therapy on loneliness in an elderly population in long-term care facilities. J Gerontol A Biol Sci Med Sci, 57(7): M428-32.

Bernabei V, De Ronchi D, La Ferla T et al. (2013) Animal-assisted interventions for elderly patients affected by dementia or psychiatric disorders: a review. J Psychiatr Res, 47(6): 762-73.

Brennan J (2014) Service animals and emotional support animals: where are they allowed and under what conditions? Houston, TX: Southwest ADA Center. [Accessed: 3 July 2017] Available from adata.org/publication/service-animals-booklet

Brodie SJ, Biley FC, Shewring M (2002) An exploration of the potential risks associated with using pet therapy in healthcare settings. J Clin Nurs, 11(4): 444-56.

Brown SM, Beesley SJ, Hopkins RO (2016) Humanizing intensive care: theory, evidence, and possibilities. In: Vincent, JL, ed. Annual Update in Intensive Care and Emergency Medicine 2016. Cham: Springer International, pp. 405-20.

Delta Society (2003) Standards of practice for animal-assisted activities and therapy. Renton, WA: Delta Society.

Delta Society 2006 - should this be Delta Society (2005) Introduction to animal assisted activities and therapies. Renton, WA: Delta Society.

Halm MA (2008) The healing power of the human-animal connection. Am J Crit Care, 17(4): 373-6.

Hoffmann AO, Lee AH, Wertenauer F et al. (2009) Dog-assisted intervention significantly reduces anxiety in hospitalized patients with major depression. European Journal of Integrative Medicine, 1(3), pp. 145-148.

Kruger KA, Serpell JA (2006) Animal-assisted interventions in mental health: definitions and theoretical foundations. In: Fine AH, ed. Handbook on animal-assisted therapy: Theoretical foundations and guidelines for practice, 2nd ed. San Diego, CA: Academic Press, pp. 21-38.

Lee D, Higgins PA (2010) Adjunctive therapies for the chronically critically ill. AACN Adv Crit Care, 21(1), pp. 92-106.

For full references, please email editorial@icumanagement.org or visit https://iii.hm/de9

Todd Dorman

Senior Associate Dean for Education Coordination
Associate Dean for Continuing Medical Education
Professor and Vice Chair for Critical Care
Department of Anesthesiology & Critical Care Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland, USA

ICU Management & Practice Editorial Board Member

tdorman@jhmi.edu

@tdorman12

From command and control to modern approaches to leadership

Historical command and control approaches to leadership fail in building relationships and engendering engagement and thus do not enhance performance like modern approaches to leadership.

Historically, leadership in medicine was taught and practised in an approach akin to the military paradigm of command and control. It was believed that given the need to respond to emergencies in a coordinated fashion a hierarchical approach to management was not only beneficial but required. Such a historical leader was not to be questioned and so the leadership style was both hierarchical and autocratic. Many of these autocratic leaders believed that if they held the most risk, then they should wield the most power and control. Unfortunately that autocratic approach leads to uncoordinated care processes, as each domain only needs to be responsive to its leader. The command and control approach simply does not get the best out of our team members as they are not valued except in how they respond to commands. It also fails to keep the patient and family needs central to decision making.

When something goes wrong, and it will, the historic approach is associated with assigning blame to an individual and thus misses the fact that most events are the fault of the system. In a command and control system these unwanted events should actually be assigned to the leader and not to the staff who happen to be involved in a "not if, but when" situation. In truth, in such a system the leader rarely accepts responsibility. Thus blame becomes the mode of operation and trust is eroded. Blame systems also cause some team members to worry so much about decision-making that they often become paralysed. Unfortunately, indecision, especially in an intensive care unit, can be quite harmful to patients who often require quick decisions.

The staff of such a team may be dedicated to patient care, but they are not fully engaged. Since engagement translates directly into performance, the team cannot achieve the same levels of quality and safety that it might otherwise be able to achieve. Too often, in such a paradigm the leader perceives a high level of respect when in fact they are mistaking fear for respect. Thus the very approach, command and control, actually leads to a lower level of performance and this means that it simply cannot achieve the outcomes that patients and their families deserve. There is a famous saying about raising children, "it takes a village" and the truth be told, the same can be said about high-quality medical care. A leader at the bedside wants and needs the input of every team member, including the family. Autocratic approaches simply diminish creativity and engagement and thus performance.

Consequently, new approaches to leadership need to be sought and taught. The need for this should not surprise us. Healthcare is not static, knowledge constantly increases, and optimal approaches to diagnosis and treatment constantly change. Leadership models change as well.

According to data from the Joint Commission on Accreditation of Healthcare Organizations, communication problems/failures are the leading cause of sentinel events, medication errors, delays in treatment and infection-associated events. For optimal patient outcome, the healthcare team needs a leader who brings out the best in every member. It can be safely stated that high-performing teams require a leader who does not try to be a hero, but strives to be a multiplier. A leader who creates an open environment that supports and values open respectful communication. Yes, teams need leaders and critical moments require decision-making under the duress of time, but even in those most stressful of times, using everyone's eyes, ears, and experience can and will enhance performance. Leaders who help the team flourish garner respect.

Understanding modern leadership requires that we appreciate the differences between a manager and a leader. The attributes associated with a manager include authoritarian, work-focused, planning and budgeting, control, has subordinates, tends to maintain status quo and aims to do things right. A leader innovates, is charismatic, people-focused, sets direction for planning, develops new ideas, imbues trust and does the right thing. In many circumstances in healthcare, clinicians are asked to do both roles simultaneously, creating confusion for staff and the individual as it may not always be clear which role the person is playing. Thus, when possible, it is best to separate these into distinct roles.

A modern leader strives to make every

member of the team feel appreciated and valued. Such a leader avoids using descriptors like "I" and "mine" and instead uses 'we" and "our". In meetings they ask for input before offering their opinion so as to avoid stealing a team member's thunder or biasing the discussion. If a team member feels that they are not valued the modern leader helps that individual participate in creating solutions, so that they can be an active part of the solution and not the problem. This type of leader understands the importance of relationships in achieving results.

The modern leader focuses at strengths while admitting there are barriers. This sounds easy, but it is not. Too often, we only see the reasons that things can't be changed or improved. Team members may have a significant amount of pent-up frustration from having tried to facilitate change but having failed or perceiving that the system failed them. Getting everyone to focus on the positive requires practice. It requires a leader to be empathetic. Leaders must appreciate that although things may not have been different in the past, by facilitating and coaching everyone into being co-creators, only then will change, improvement and innovation flourish. These additional inputs are beneficial in such complex systems.

This philosophy affects how they see events and how they structure and conduct meetings. Thus the modern leader spends the majority of time in meetings on identifying what works and what the team does well so that those elements are translated into other domains. The team is encouraged to build from success instead of focusing at the negative. Then, only after working through the strengths, is everyone asked to identify 1-2 barriers. This avoids the barrier discussion from being up front, encourages folks to think about solutions first and not the negative, yet still recognises that barriers exist and need to be addressed. The agenda should be crafted in a manner that mirrors this approach of learning from the positives before getting to the negatives (barriers).

In meetings, a true leader avoids speaking up first as this colours and can dampen subsequent discussions, as some present will be reluctant to speak up in a manner that might contradict the "leader". In addition, by encouraging others to speak up first, a modern leader is allowing the team to work to a solution and thus increasing the team members' sense of self-worth and supporting their work effort, creativity and engagement.

> **"high-performing teams require a leader who does not try to be a hero, but strives to be a multiplier"**

There is an important parallel to mention. Education has been conducted by the "sage on the stage". The sage holds all of the knowledge and their job is to push it to you. Education research has shown that this places the learner in a passive role in which they learn much less effectively. The modern education approach is for the educator to be more a coach, a facilitator and an orchestrator. Similarly, the command and control leader needs to morph into one that does not require their minions to merely passively respond, but to be actively involved and engaged. This easily translates to the bedside where the modern leader engages all members of the team, including family, to facilitate their understanding of the patient and the team's understanding of the complex issues at play in critical illness.

In conclusion, modern leaders are different from the iteration of command and control leaders. They are empathetic and they work hard to multiply the impact of all team members. They are more coach than simply Delphi. Given this coaching role, I will quote a National Basketball Association coach, Steve Kerr, who recently stated in an interview published in *Sports Illustrated* and written by Chris Ballard, "The people to me who are the most powerful leaders are the ones who have great talent in whatever their field is, great conviction in their ability to teach it and act it, but an awareness and a humility and compassion for others." Clearly there is a new path to leading and maximising performance of our teams all in the name of enhanced patient and family care. Importantly, while this approach helps enhance patient and family care, it also can help empower our team and thus can have impact on the rates of PTSD and burnout in our teams. ■

Suggested readings

Books

Wiseman L (2010) Multipliers: how the best leaders make everyone smarter. New York: Harper Collins.

Jennings KR, Stahl-Wert J (2016) The serving leader: five powerful actions to transform your business, team, and community. 2nd ed. Oakland, CA: Berrett-Koehler Publishers.

Articles

Plsek PE, Wilson T (2001) Complexity, leadership, and management in healthcare. BMJ, 323: 746-9.

Millward LJ, Bryan K (2005) Clinical leadership in health care: a position statement. Int J Health Care Qual Assur Inc Leadersh Health Serv, 18(2-3): 13-25.

Ballard C (2017) Steve Kerr's absence: the true test of a leader. Sports Illustrated, May 6.

Zaleznik A (2004) Managers and leaders: are they different? Harv Bus Rev, 82(1): 74-81. [Accessed: 3 July 2017] Available from **hbr.org/2004/01/managers-and-leaders-are-they-different**

Website

Robert K. Greenleaf Center for Servant Leadership **greenleaf.org**

Tom J. Pollard
Research Scientist
Massachusetts Institute of Technology
Cambridge, USA

tpollard@mit.edu

@tompollard

Leo Anthony Celi
Intensivist and Principal Research Scientist
Massachusetts Institute of Technology
Cambridge, USA

Beth Israel Deaconess Medical Center
Boston, USA

lceli@mit.edu

Enabling machine learning in critical care

Critical care units are home to some of the most sophisticated patient technology within hospitals. In parallel, the field of machine learning is advancing rapidly and increasingly touching our lives. To facilitate the adoption of machine learning approaches in critical care, we must become better at sharing and integrating data. Greater emphasis on collaboration—outside the traditional "multidisciplinary" realm and into the engineering, mathematical, and computer sciences—will help us to achieve this. Meanwhile, those at the forefront of the health data revolution must earn and maintain society's trust and demonstrate that data sharing and reuse is a necessary step to improve patient care.

Critical care units are home to some of the most sophisticated patient technology within hospitals. Devices such as vital sign monitors, mechanical ventilators and dialysis machines, to name a few, are used to support patients whose bodies need time to recover and repair. Data, a by-product of technology, contains information with the potential to improve our understanding of health and disease. Outside critical care units, we are seeing increasing adoption of digital health systems in place of the paper-based systems of the past.

In parallel, the field of machine learning is advancing rapidly and increasingly touching our lives. Algorithms built upon large volumes of data have beaten world champions in the complex game of Go, driven cars on the open roads, and matched doctors in diagnosing skin cancers (Esteva et al. 2017) and diabetic eye conditions (Gulshan et al. 2016).

With these advances, are we now on the cusp of transformed, algorithm-driven care? Not yet, it would seem. In critical care, and medicine as a whole, the massive troves of data needed to pour into machine learning algorithms are difficult to find and access. For the development of machine learning-based approaches to care, data must first be properly archived, integrated across data sources and shared for reuse. Most hospitals have a long way to go in this regard. Data is still treated as a currency for clinical researchers to build careers, harming efforts to combine data to an extent that can fuel progress. The absence of incentives for data integration and data sharing has hindered us from understanding health and disease in new ways from analysing 'real-world' data collected in the process of care. Too many of our study models still rely on either absurdly small datasets or on large-scale but coarse registry data devoid of the rich details that are required to unleash the value of machine learning.

With funding from the National Institutes of Health, the MIT Laboratory for Computational Physiology (MIT-LCP) develops and maintains the publicly available Medical Information Mart in Intensive Care (MIMIC), a database of patients admitted to the intensive care units of a large teaching hospital of the Harvard Medical School. The current version, MIMIC-III, contains data associated with 53,423 distinct hospital admissions for adult patients admitted to critical care units between 2001 and 2012 (Johnson et al. 2016). Data include vital signs, medications, laboratory measurements, charted notes, billing codes and out-of-hospital survival data. With over 4,000 users in academia and industry from over 30 countries. MIMIC-III has been used for clinical research studies, exploratory and validation analyses performed by pharmaceutical and medical technology companies, as well as university, conference and online courses, tutorials and workshops. At least 24 courses in the United States alone use the database to teach concepts in machine learning, medical informatics and biostatistics.

Spurred by the success of MIMIC, MIT-LCP recently released the eICU Collaborative Research Database in collaboration with Philips Healthcare, comprising de-identified health data associated with over 200,000 critical care admissions from patients admitted to >200 hospitals throughout the United States between 2014-2015. The dataset is itself a subset drawn from a pool of nearly 3 million ICU admissions and provides a unique and invaluable resource for health research and education. Like MIMIC-III, the database includes detailed clinical data such as vital signs, pharmacy medication orders, laboratory results and severity of illness scores, giving researchers comprehensive insights into patient care. The database presents an opportunity to assess

heterogeneity in treatments, patient populations and settings, which was not possible with large single-site research databases such as MIMIC-III.

To encourage research transparency and collaboration around the databases, MIT-LCP creates and supports collaboratively maintained, open code repositories. For example, the MIMIC Code Repository is a centralised code base for generating reproducible studies on the MIMIC-III dataset (MIMIC in press). All code is made open source under an MIT License and is freely available online (**github.com/MIT-LCP/mimic-code**). Executable documents reproduce published studies end-to-end, providing a template for future researchers to replicate. The repository's issue tracker enables community discussion about the data and concepts, allowing users to collaboratively improve the resource. Consistent application of the same code for underlying concepts is a key step in ensuring research studies in critical care are comparable and reproducible.

But it is not enough to create high-resolution databases to propel the application of machine learning in critical care medicine. The most daunting challenge, as with most complex problems of our time, is the lack of collaboration across the key players who represent the disciplines and who continue to work in their own silos (Celi et al. 2016a). To this end, MIT-LCP organises critical care datathons, a portmanteau of data + hackathon, focusing the application of the hackathon model on data analytics (Aboab et al. 2016; Celi et al. 2016b). The goal of these datathons is to unify clinical experts, data scientists, statisticians and those with domain-specific knowledge to brainstorm ideas and contribute clinically relevant research.

Datathons

During the past year, MIT-LCP has helped to organise and host several international datathons to gain new insights from routinely collected patient data. The events were held in Beijing in October 2016 (funded by the People's Liberation Army General Hospital), London in December 2016 (funded by the UK Intensive Care Society and the MIT International Science and Technology Initiatives Global Seed Fund), Melbourne in March 2017 (funded by the Australian and New Zealand Intensive Care Society, Alfred Hospital and Philips Healthcare), Sao Paulo in May 2017 (funded by the Hospital Israelita Albert Einstein and the MIT Brazil Seed Fund) and Singapore in July 2017 (funded by Merck Sharpe & Dohme and the National University of Singapore).

> "power of freely accessible data repositories for crowdsourcing knowledge creation and validation"

Bringing together clinicians (including nurses, pharmacists and therapists) and data scientists at datathons serves to demonstrate the value of each other's expertise. We have found these events to be an important tool in demonstrating the power of freely accessible data repositories for crowdsourcing knowledge creation and validation. Perhaps most importantly, they have generated interest amongst participants to contribute new, high-resolution critical care databases to the research community, supplementing existing resources such as MIMIC-III and the eICU Collaborative Research Database.

For a more in-depth tutorial in secondary analysis of health records, MIT-LCP teaches a fall course at MIT on Collaborative Data Science in Medicine. Students learn the basics of research using routinely collected health data, including data extraction, processing and analysis, and acquire skills from a diverse set of fields including epidemiology, databases, statistics and machine learning. In addition, students team up with Boston-area clinicians for a course project using either MIMIC-III or the eICU Collaborative Research Database to produce novel research, often leading to publication in a clinical journal. An open access textbook accompanies the course and has been downloaded more than 90,000 times since its publication in October 2016 (Celi et al. 2016c).

Change is on the horizon with growing interest in digital health, the application of machine learning on health data and the dawn of artificial intelligence to assist healthcare providers and patients. In the United States alone, venture capital investments in digital health grew at an annual rate of 30% from 2011 to 2016 and last year totalled US$4.2 billion (Tecco 2017). More large companies, from Apple, Microsoft, IBM, Alphabet (Google's parent), Merck, Aetna, to UnitedHealth Group (through its Optum subsidiary), are investing in digital health products (Swanson 2016; CB Insights 2016; Bergen 2015). But for a true health data revolution to occur in healthcare, the environment—the technology, the policies, and the people, both providers and patients—needs to be supportive of change.

Within hospitals we will need to begin adapting culture and education to prepare for the changes to come. Greater emphasis on collaboration – outside the traditional "multidisciplinary" realm and into the engineering, mathematical, and computer sciences – will help us to create the right environment for a move towards algorithm-driven care. Meanwhile, those at the forefront of the health data revolution must earn and maintain society's trust and demonstrate that data sharing and reuse is a necessary step to improve patient care.

Conflict of interest

The authors have received funding from Philips and Merck. ■

References

Aboab J, Celi LA, Charlton P et al. (2016) A datathon model to support cross-disciplinary collaboration. Sci Transl Med, 8(333): 333ps8.

Celi LA, Davidzon G, Johnson AE et al. (2016) Bridging the health data divide. J Med Internet Res, 18(12): e325.

Esteva A, Kuprel B, Novoa RA et al. (2017) Dermatologist-level classification of skin cancer with deep neural networks. Nature, 542: 115-8.

Gulshan V, Peng L, Coram M et al. (2016) Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA, 316(22): 2402-10.

Johnson AEW, Pollard TJ, Shen L et al. (2016) MIMIC-III, a freely accessible critical care database. Scientific Data, 3: 160035.

Johnson AEW, Stone DJ, Celi LA et al. (2017) The MIMIC code repository: enabling reproducibility in critical care research. JAMIA: Journal of the American Medical Informatics Association. In Press. doi: 10.1093/jamia/ocx084

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

AGENDA

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

OCTOBER

3-5 Critical Care Canada Forum 2017
Toronto, Canada
https://iii.hm/d8j

11-13 ANZICS/ACCCN Annual Scientific Meeting 2017
Broadbeach, Australia
https://iii.hm/d8l

21-25 ANESTHESIOLOGY® 2017
Boston, USA
https://iii.hm/d8n

NOVEMBER

2-4 6th Annual Johns Hopkins Critical Care Rehabilitation Conference
Baltimore, USA
https://iii.hm/d8o

5-7 European Airway Management Congress 2017
Berlin, Germany
https://iii.hm/d8p

9-10 ESA Focus Meeting on Perioperative Medicine
Tel Aviv, Israel
https://iii.hm/d8q

8-11 13th World Congress of Intensive and Critical Care Medicine
and XXII Brazilian Congress of Intensive Care Medicine
Rio de Janeiro, Brazil
https://iii.hm/d8r

11-12 5th European Conference on Weaning & Rehabilitation in Critically Ill Patients
London, UK
https://iii.hm/d8s

14-16 Echocardiography for Hemodynamic Monitoring 2017
Brussels, Belgium
https://iii.hm/d8t

17 World Day of the Critical Lung
Online
https://iii.hm/d8u

22-24 Difficult Airway Society Annual Scientific Meeting 2017
London, UK
https://iii.hm/d8v

23-25 6th International Fluid Academy Congress 2017
Antwerp, Belgium
https://iii.hm/d8w

28-30 ATHENA 2017 International Conference
Athens, Greece
https://iii.hm/d8x

DECEMBER

4-6 Intensive Care Society State of the Art Meeting 2017
Liverpool, UK
https://iii.hm/d8y

6-8 DIVI-Kongress 2017
Leipzig, Germany
https://iii.hm/d8z

6-8 23rd Postgraduate Refresher Course on Cardiovascular and Respiratory Physiology Applied to ICM
Brussels, Belgium
https://iii.hm/d90

6-9 Emirates Society of Emergency Medicine Scientific Conference
Dubai, UAE
https://iii.hm/d91

10-13 Update on monitoring in the acutely ill patient: An integrated approach
Rome, Italy
https://iii.hm/d92

JANUARY

17-19 ICU Leadership 2018
Brussels, Belgium
https://iii.hm/d93

ICU
MANAGEMENT & PRACTICE

PRODUCTION, PRINTING AND DISTRIBUTION
Printed in Hungary by ABEL Printing
Total classic and digital distribution: 21,500
ISSN = 1377-7564

VERIFIED CIRCULATION
according to the standards of International Business Press Audits.

ICU Management & Practice is independently audited by AKC.

Faster clinical results

to better decide **on-the-spot**

Minicare I-20 is ready where you are, wherever you need to rapidly assess patients showing signs of critical heart diseases. Our novel near-patient tests for cTnI and BNP provide lab-comparable results within 10 minutes so you can deliver more effective, more personalized care where it's needed most.

innovation + you

Minicare I-20
www.philips.com/minicare

PHILIPS