ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 19 - ISSUE 3 - AUTUMN 2019

SPECIAL SUPPLEMENTS

CSL Behring Symposium Report

Factor Concentrates in the Perioperative Management of Coagulopathy

Nestlé Nutrition Institute Symposium Report

The Expanding Boundaries of ICU Nutrition

Nutrition

New ESPEN Guidelines for Nutrition in the Critically Ill: Help, What Happened!? *M. Casaer, G. Van den Berghe, J. Gunst*

New Trends in ICU Nutrition, *V. Fraipont, J.C. Preiser*

Emerging Concepts in Nutritional Therapy for the Critically Ill Child, *N. Mehta*

Obesity and Nutrition in Critical Illness, *E. Ridley, M. Chapman, K. Lambell, S. Peake*

Objective Malnutrition Diagnosis and Personalised Nutrition Delivery in the ICU, *P. Wischmeyer, J. Molinger*

The Role of Speech and Language Therapy Supporting Nutritional Management in ICU, *J. McRae*

PLUS

Virtual Reality in the Intensive Care Unit: State of Play and Future Prospects, *V. Beaucote, O. Clovet, A. Esnault, T. Lescot*

Pre-packed Critical Care Drug Pouch for Acute Patient Care: Consensus, Simulation Testing and Recommendations, *A. Gandhi, W. Chan, C. Meyers, P. Barach, F. Rubulotta*

Knowledge Transfer to Improve Outcomes in Critically Ill Immunocompromised Patients, *E. Azoulay*

Challenges in the Management of the Critically Ill Patient, *M. Antonelli*

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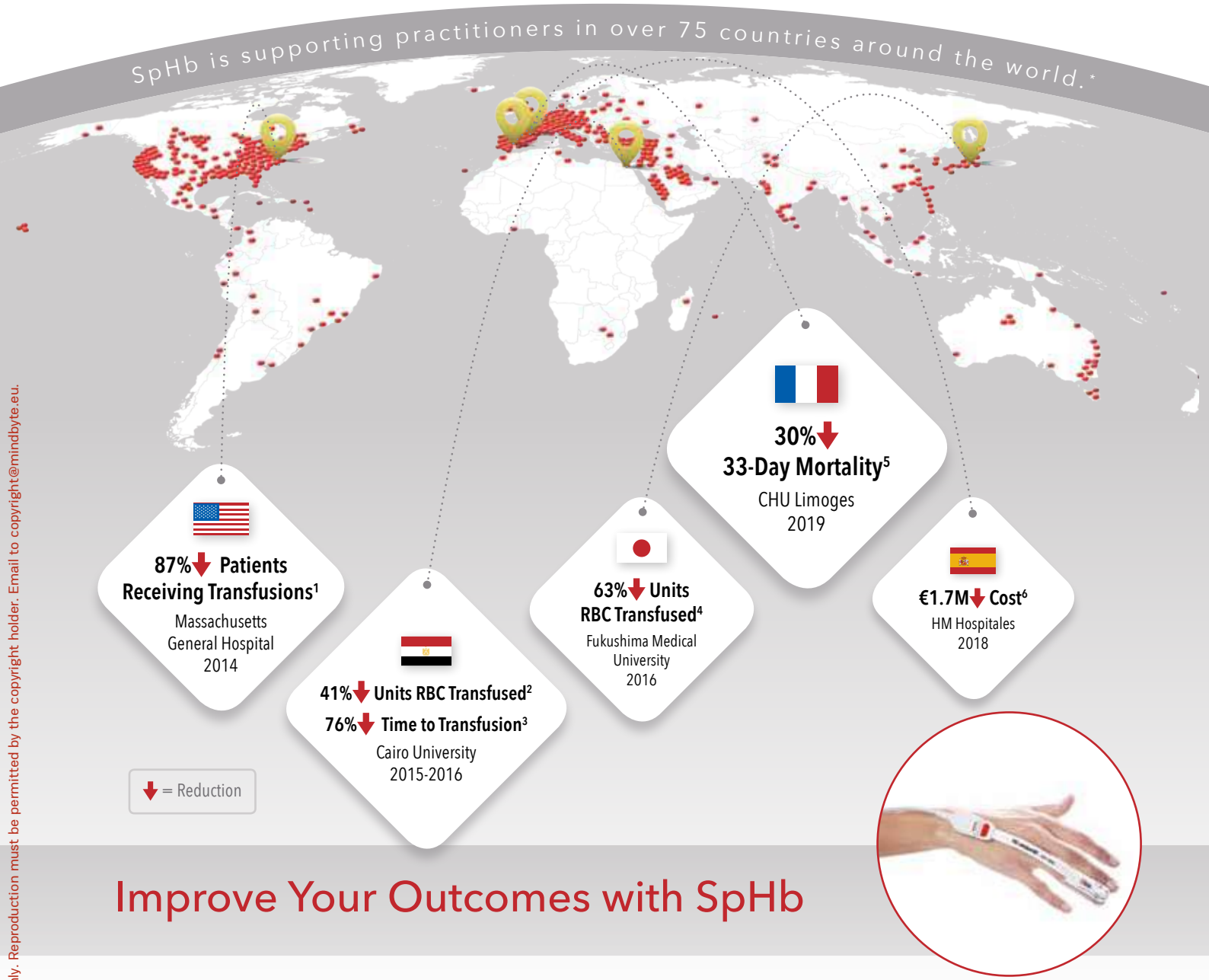

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[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9. [2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4. Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer. [3] Kamal A, et al. *Open J of Anesth.* 2016 Mar; 6, 13-19. [4] Imaizumi et al. *Proceedings from the 16th World Congress of Anaesthesiologists*, Hong Kong. Abstract #PR607. [5] Cros et al. *J Clin Monit Comput.* Aug 2019: 1-9. Study utilised a goal-directed fluid therapy protocol with PVi® in conjunction with a blood transfusion protocol based on SpHb. [6] Ribed-Sánchez B, et al. *Sensors* (Basel). 2018 Apr 27;18(5). pii: E1367. * Data on file.

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NUTRITION

The critically ill patient is often unable to feed by mouth. This condition, in some patients, can range from days to months. It is imperative that these patients receive macronutrients either through enteral or parenteral nutrition. If they don't, there is a risk of an energy deficit that could lead to loss of lean body mass and subsequently, other adverse outcomes. Muscle wasting and weakness due to lack of nutrition during critical illness also increase the risk of prolonged mechanical ventilation, and a longer period of immobilisation.

Nutrition in the ICU presents a number of challenges for clinicians. There is a wide variation in the type of patients that doctors in the ICU have to deal with - from those who have just been through surgery to those admitted because of emergencies, trauma, sepsis or respiratory failure. There are patients who are extremely young to those who are elderly and frail. Each type of patient requires individual assessment and a specific approach. That is the key to nutritional management in the ICU.

Our cover story **Nutrition** discusses the most effective strategies for managing nutrition in critically ill patients and presents an overview of the key guidelines for nutrition management. Our contributors talk about the basic fundamentals of nutritional support for the critically ill and review nutritional goals, daily nutritional requirements, nutritional strategies, indications, contraindications, and the impact of nutrition on patient outcomes.

Michael P. Casaer, Greet Van den Burghe, and Jan Gunst discuss the new ESPEN guidelines for nutrition in critical illness while Vincent Fraipont and Jean-Charles Preiser provide an overview of the new trends in ICU nutrition.

When discussing the need to address nutrition provision in specific patient populations, Nilesh Mehta presents a comprehensive review of the emerging concepts in nutritional therapy for the critically ill child while Emma J. Ridley, Marianne Chapman, Kate Lambell and Sandra Peake talk about the role of nutrition in obese critically ill patients.

Paul E. Wischmeyer and Jeroen Moligner highlight the importance of objective malnutrition diagnosis and personalised nutrition delivery in the ICU, and Jackie McRae discusses the role of speech and language therapy for supporting nutritional management in intensive care.

In our Informatics and Technology section, Victor Beaucote, Olivier Clovet, Amaury Esnault, and Thomas Lescot present an overview of the practical uses of virtual reality in the ICU, the benefits it can provide, and future prospects.

In our Matrix section, Ajay Gandhi, Wei Yee Chan, Cheryl Meyers, Paul Barach, and Francesca Rubulotta propose standardisation and consolidation of agreed drugs and equipment into a compact pre-packed critical care drugs pouch for acute patient care.

In our Management section, Élie Azoulay provides an overview on sharing information, improving clinician skills, and transferring knowledge to ICU specialists about the care of immunocompromised patients.

Our interview section features Massimo Antonelli, Professor of Intensive Care and Anesthesiology at Università Cattolica del Sacro Cuore in Rome, Italy. Prof. Antonelli's scientific fields of interest and research include noninvasive ventilation, mechanical ventilation, ARDS, shock, sepsis, and infections. He spoke to ICU Management & Practice about the major challenges in the management of the critically ill patient.

The nutritional status of a critically ill patient can often be difficult to assess. Following a structured approach and determining nutritional requirements based on specific patient characteristics can help improve the delivery of nutrition in the ICU. It is important to understand that poor nutrition can lead to poor outcomes in critical illness. It is time to challenge old-fashioned concepts and to implement nutritional support strategies that can ensure adequate nutritional support in the ICU, promote early mobilisation, improve quality of life and offer better long-term outcomes for the critically ill patient.

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

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Factor Concentrates in the Perioperative Management of Coagulopathy

CSL Behring Special Symposium Euroanaesthesia 2019 - Vienna, Austria

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Supplement in collaboration with CSL Behring

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Pathophysiology of Trauma and Revised European Trauma Guidelines

The fifth edition of the European Trauma Treatment Guidelines that have already been cited 1650 times and downloaded from the original home page nearly 600,000 times.

The European trauma treatment guidelines have significantly changed the treatment modalities of trauma patients around the world. The guidelines have also been endorsed by major European professional societies including European Society of Anaesthesiology (ESA), European Society of Intensive Care Medicine (ESICM), European Shock Society (ESS), European Society for Trauma and Emergency Surgery (ESTES), European Society for Emergency Medicine (EuSEM), Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA). There is, therefore, profound consensus with respect to these guidelines.

This updated version of the guidelines considers all the scientific evidence that has been produced during the last three years as well as evidence from current clinical practice. The existing suggestions and recommendations were revised by a group of experts, mainly delegates of European professional societies

In the fifth version, there is more elaboration on the pathophysiology of trauma-induced coagulopathy. The organisation of the guidelines reflects the decision-making process along the patient pathway and less the treatment modalities. There are now nine chapters which are comparatively more patient and problem-oriented. The former chapter on resuscitation measures has been reorganised into three separate chapters (Chapters VI, VII, VII). **Table 1** outlines the major issues/topics discussed in the new chapters (Spahn et al. 2019).

Key Recommendations in the Revised Guidelines

Some of the key recommendations in the revised guidelines include the following (Spahn et al. 2019):

- Routine practice should include the early and repeated monitoring of haemostasis, using either a combined traditional laboratory determination [prothrombin time (PT), platelet counts and fibrinogen] and/or point-of-care (POC) PT/international normalised ratio (INR) and/or a viscoelastic method (VEM). As per the new addition, laboratory tests are graded equally to the VEM test, and the Activated Partial Thromboplastin Time (APTT) is deleted because it is unspecific and does not offer any interpretation in the context of major trauma. Also, early and repeated are both very important terms in this recommendation because it is important to get an idea about the problem early on in order to determine whether it has been treated or whether there is a need for a second round of treatment with the same or with other treatment modalities.
- Patients treated or suspected of being treated with anticoagulant agents should be screened.
- Tranexamic acid (TXA) should be administered to the trauma patient who is bleeding or at risk of significant haemorrhage as soon as possible and within 3h after injury at a loading dose of 1g infused over 10 minutes, followed by an IV infusion of 1g over 8 hours. This is still in place as the last version.
- Protocols for the management of bleeding patients should consider the administration of the first dose of TXA en-route to the hospital. The important thing is to give it as early as possible.
- The administration of TXA should not await results from a viscoelastic assessment. It should always be given and it should be given as early as possible.
- In the initial management of patients with expected massive haemorrhage, it is recommended that one of the two following strategies should be followed:
  1. FFP (fresh frozen plasma) or pathogen-inactivated FFP in an FFP:RBC (red blood cells) ratio of at least 1:2 as needed.
  2. Fibrinogen concentrate and RBC.
- As per the revised guidelines, both measures are graded equally and should be determined based on a goal-directed strategy.
- Resuscitation measures should be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM.
- Treatment with fibrinogen concentrate or cryoprecipitate should be initiated if major bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤1.5 g/L).
- Reversal of the effect of antithrombotic agents in patients with ongoing bleeding is recommended. The need for reversal should be weighed against the prothrombic state of the patient. This is because patients taking antithrombotic medications have an

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- **Chapter VI: Further goal-directed coagulation management**
  - Goal-directed therapy (R25)
  - FFP-based strategy (R26)
  - CFC-based management (R27), including the use of FXIII
  - Fibrinogen supplementation (R28)
  - Platelet administration (R29)
  - Calcium (R30)
  - rFVIIa (R31)
- **Chapter VII: Reversal of antithrombotic agents**
  - Monitoring and treatment (VKA and DOACs: R33, R34, R35)
  - Monitoring and treatment of trauma patients who are being treated with platelet inhibitors (R36)
- **Chapter VIII: Thromboprophylaxis**
  - Recommendation for the prophylactic prevention of thromboembolic complications (R37) in major trauma patients
  - Which is increasingly recognised as important, particularly in patients treated prior to traumatic injury with oral anticoagulants and/or platelet inhibitors
- **Chapter IX: Guideline implementation and quality control**
  - Encouragement of local implementation (R38) of evidence-based guidelines for the management of the bleeding patient following traumatic injury
  - Local quality and safety management systems (R39) specifically assess key measures of bleeding control and outcome

Table 1. New Chapters in the Fifth Version of the European Trauma Treatment Guidelines (Spahn et al. 2019).

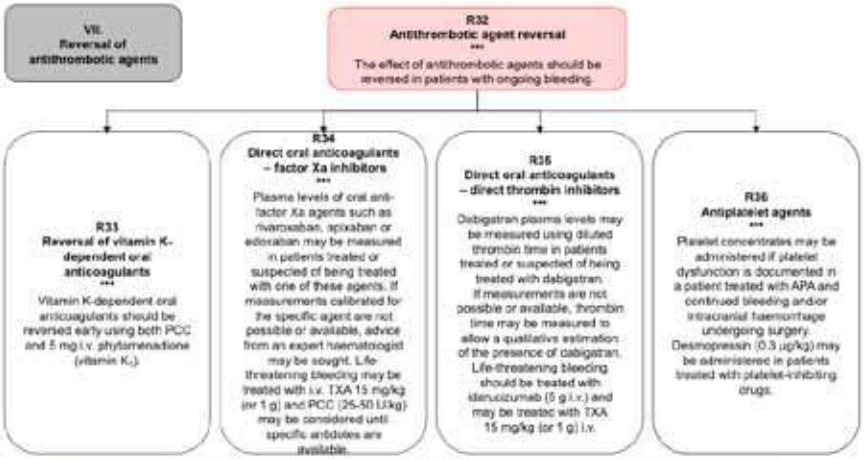

Figure 1. Reversal of antithrombotic agents (Spahn et al. 2019).

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underlying thrombotic risk. Full reversal of the anticoagulant is only justified if there is life-threatening bleeding (ema.europa.eu/en/medicines/human/summaries-opinion/ondexxya). This is a new chapter in the guidelines, details of which are outlined in **Figure 1** (Spahn et al. 2019).

- Appropriate thromboprophylaxis should be initiated as soon as possible after bleeding has been controlled.
- In the bleeding trauma patient, the emergency reversal of vitamin K-dependent oral anticoagulants is recommended with the early use of both prothrombin complex concentrates (PCC) and 5mg IV phytomenadione (vitamin K1).
- Measurement of plasma levels of oral direct anti-factor Xa agents such as apixaban, edoxaban, or rivaroxaban should be done in patients treated or suspected of being treated with one of these agents.
- Measurement of anti-Xa activity should be calibrated for the specific agent. If measurement is not possible or available, advice from an expert haematologist should be sought.
- If bleeding is life-threatening, TXA 15 mg/kg (or 1g) should be administered intravenously, and the use of PCC (25-50 U/kg) be considered until specific antidotes are available.
- Dabigatran plasma levels should be measured using diluted thrombin time in patients treated or suspected of being treated with dabigatran.
- If measurement is not possible or available, standard thrombin time should be measured to allow a qualitative estimation of the presence of dabigatran.
- If bleeding is life-threatening in those receiving dabigatran, patients should be treated with idarucizumab (5g intravenously) and with TXA 15 mg/kg (or 1 g) intravenously. ■

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Abbreviations

APTT	activated partial thromboplastin time
FFP	fresh frozen plasma
INR	international normalised ratio
PCC	prothrombin complex concentrates
POC	point-of-care
PT	prothrombin time
RCB	red blood cells
TXA	tranexamic acid
VEM	viscoelastic method

Key Points

- Injured patients should be transported quickly and treated by a specialised trauma centre whenever possible.
- Measures to monitor and support coagulation should be initiated as early as possible and used to guide a goal-directed treatment strategy.
- A damage control approach to surgical intervention should guide patient management.
- Coagulation support and thromboprophylactic strategies should consider trauma patients who have been pretreated with anticoagulants or platelet inhibitors.
- Local adherence to a multidisciplinary, evidence-based treatment protocol should serve as the basis of patient management and undergo regular quality assessment.

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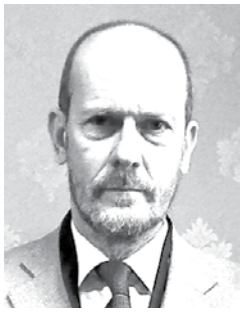

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Coagulopathy During Cardiac Surgery: The Role of Factor Concentrates

The EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery.

The EACTS/EACTA guidelines were published jointly by the Society of Cardiothoracic Anesthesia and Cardiac Surgery for patient blood management. In the bleeding patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions. However, the prerequisite is a bleeding patient. In patients where bleeding is related to coagulation factor deficiency, prothrombin complex concentrates (PCC), or fresh frozen plasma (FFP) administration should be considered to reduce bleeding and transfusions (Boer et al. 2017).

As far as clinical evidence is concerned, there is conflicting data with respect to fibrinogen supplementation. In a study conducted about four years ago, patients were randomised to receive either fibrinogen or placebo. This was a non-pragmatic trial conducted in an artificial environment where patients that had bleeding due to other reasons were excluded. The goal was to demonstrate that a first-line fibrinogen supplementation would avoid the need for FFP and would reduce the need for any kind of transfusions. The primary endpoint was achieved (**Figure 1**), and the group treated with fibrinogen had zero need for FFP or platelets (Ranucci et al. 2015).

However, the Randomized Evaluation of Fibrinogen vs. Placebo in Complex Cardiovascular Surgery (REPLACE) study provided different results. Fibrinogen administration resulted in higher reduction of bleeding (**Figure 2**). Medication was administered to patients with a 5 minute bleeding mass of 60-250g after separation from bypass and

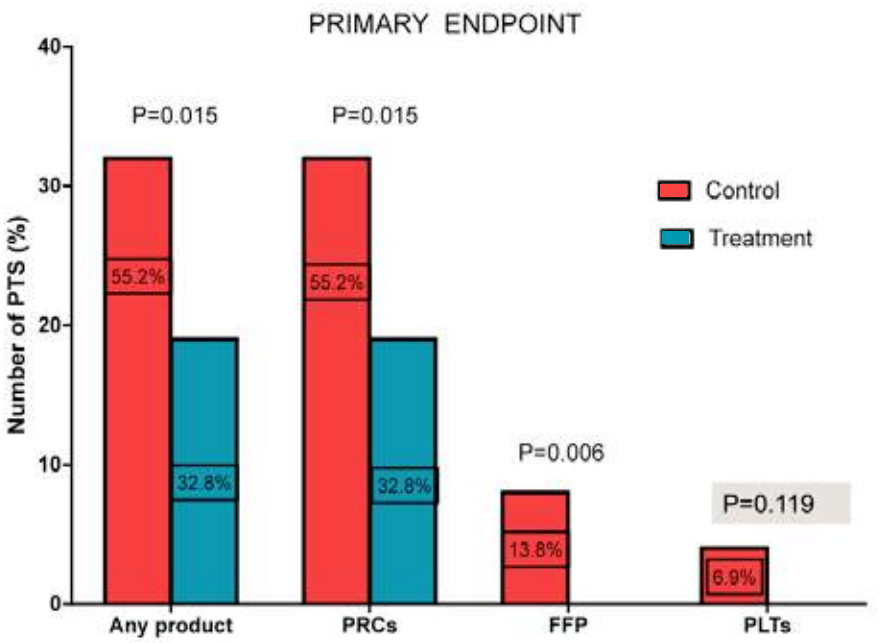

Figure 1. Fibronogen concentrate supplementation after complex cardic surgery (Ranucci et a. 2015).

> **in the bleeding patient with a low fibrinogen level, fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions**

surgical haemostasis. Study findings did not demonstrate a reduction in total units of allogenic blood products (ABP) [FFP, platelets, and/or RBCs] transfused over 24 hours with fibrinogen concentrate compared with placebo. Surprisingly, human fibrinogen concentrate was found to be associated with increased blood product transfusion compared to placebo (Rohe-Meyer N et al. 2016).

Yet another very well-designed study that focused on intraoperative bleeding showed different findings. Patients were randomised into two groups where they received an intravenous, single dose of fibrinogen concentrate or placebo. The primary outcome was blood loss between intervention and closure of chest. In patients with intraoperative bleeding during high-risk cardiac surgery, administration of fibrinogen concentrate resulted in no significant difference in the amount of intraoperative blood loss compared to placebo (Bilecen S. et

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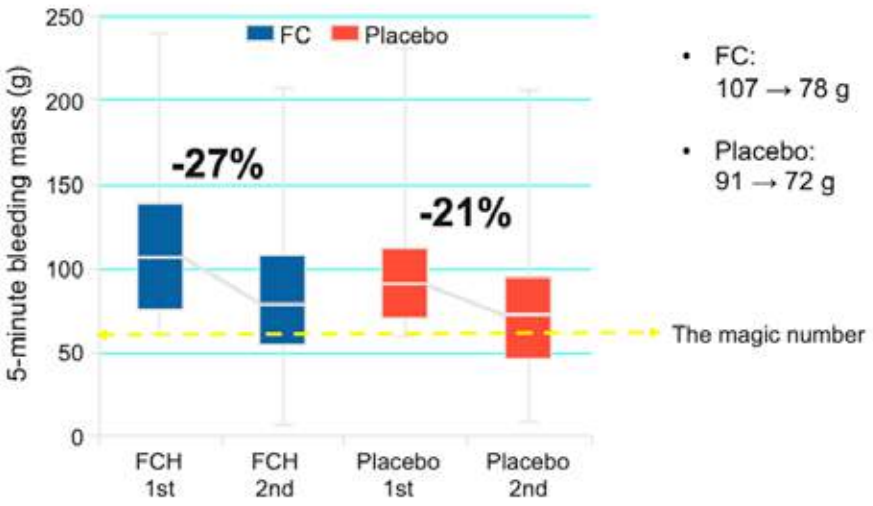

Figure 2. Fibrinogen administration resulted in higher reduction of bleeding (Rohr-Meyer N et al. 2016).
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Key Points

- FFP is a poor source of fibrinogen and prothrombin complexes.
- Cryoprecipitate is a moderately good source of fibrinogen but has multi-donor risks.
- PCC and fibrinogen are both elegant ways to replace FFP.
- In the bleeding patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions in bleeding patients with a low fibrinogen level.
- PCC or FFP administration should be considered to reduce bleeding and transfusions when bleeding is related to coagulation factor deficiency.

al. 2017). There was one problem, however. The window of observation of bleeding was incredibly short. The observation time of bleeding was six minutes. The control group bled 70 millilitres and the study group 50 millilitres.

Blood, Blood Products And Derivatives - Use In Trauma And Cardiac/Liver Surgery

There are different solutions that are available for clinicians to reduce postoperative bleeding and transfusions. Here is a quick overview of the primary ones:

Fresh Frozen Plasma (FFP)

- Poor source of fibrinogen and prothrombin complexes
- Huge quantity needed
- Increasingly not considered the best product but still largely used
- Offers benefits whenever large volumes of fluids are required (e.g. in trauma patients)
- Very inexpensive

Cryoprecipitate

- Moderately good source of fibrinogen
- Limited volume overload
- Unavailable in many countries/hospitals but still largely used
- Multi-donor risks
- Probably will become less popular in the years to come

Prothrombin Complex Concentrate (PCCs)

- An elegant way to replace FFP
- Triggered by point-of-care haemostatic testing (POC) tests
- Associated with increased thromboembolic events and acute kidney injury (AKI)
- Effective but expensive
- Use likely to moderately increase in the years to come

Fibrinogen

- The main component of clot firmness
- Elegant way to replace FFP or cryoprecipitates
- Triggered by POC (mainly rotational thromboelastometry)
- Not associated with increased thromboembolic events
- Effective but expensive
- Dose unclear (both target concentration and dose calculation)

Therefore, to answer the question as to when to supplement with fibrinogen, the guidelines recommend that in the bleeding patient with a low fibrinogen level (<1.5 g/L), fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions. In patients where bleeding is related to coagulation factor deficiency, PCC, or FFP administration should be considered to reduce bleeding and transfusions. ■

Abbreviations

ABC	allogenic blood products
AKI	acute kidney injury
FFP	fresh frozen plasma
PCC	prothrombin complex concentrates
PLT	platelets
RBC	red blood cells

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Treatment Options for Factor-Xa Inhibitor-Related Bleeding

Specific treatment options for factor Xa inhibitor-related bleeding, focusing on drugs like rivaroxaban, apixaban, and edoxaban.

Non-vitamin K oral anticoagulants (NOACs/DOACs) are direct reversible inhibitors of factor Xa. These drugs are also reversible inhibitors versus warfarin or other vitamin K antagonist that are used in Europe. Anticoagulants decrease circulating levels of factor II, VII, IX and X. In patients with acute bleeding, the concept of factor concentrates is to restore the levels of these agents. When a patient comes in on a NOAC and needs emergency surgery or is actively bleeding, two important questions must be asked. One is what's their renal function as it can have an impact on drug elimination, and the other is coagulation testing.

Measuring the effects of these new oral anticoagulants and nonvitamin K can be confusing for clinicians. There are some important caveats to consider (Heidbuchel H et al. 2013):

- Prothrombin time (PT)/ International normalised ratio (INR)/partial thromboplastin time (PTT) are relatively insensitive to the effects of anti-FXa agents and are reagent-dependent
- Normal PT and PTT do not rule out significant blood level of DOACs, especially anti-FXa agents
- In case of elevated PT, this may represent high blood levels of DOACs or coagulopathy

With respect to when to decide to potentially consider drug levels, it should be done:

- o If the patient is bleeding or there is a risk of potential overdose
- o In case of impaired renal or liver function
- o To evaluate for low level prior to surgery

Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical. The two specific state of the art reversal agents (also called antidotes) that can be used to manage a major bleed include idarucizumab and andexanet. Andexanet reverses FXa inhibitors. Once bound to andexanet, inhibitors are unable to bind/inhibit FXa (Ansell 2013). Andexanet comes in vials that require mixing, and is given as a loading dose followed by an infusion of two hours. The drug effect on reversal is about three hours (**Figure 1**). A large study was conducted, which led to the drug's approval both in the U.S. and in Europe. However, it is important to note that there is no current surgical data supporting this particular use. The drug is approved for emergency medical bleeds only, in particular, intracranial haemorrhages. Of the 352 patients in the final New England Journal of Medicine study, 64% were intracranial hemorrhage, and about 26% were GI bleeds.

> **bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy**

As demonstrated in **Figure 2**, anti–factor Xa activity among persons who had received anticoagulation treatment with apixaban or rivaroxaban was measured before and after the administration of andexanet or placebo on study day 4. Dashed lines indicate the end of administration of the bolus or infusion. Panel A shows data from participants in the apixaban study (ANNEXA-A) who received andexanet, as a 400-mg intravenous bolus, or placebo; Panel B participants in the rivaroxaban study (ANNEXA-R) who received andexanet, as an 800-mg intravenous bolus, or placebo; Panel

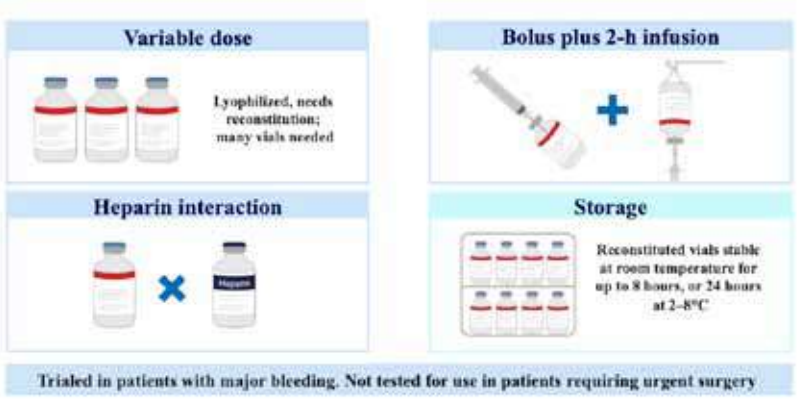

Figure 1. Andexanet Rx: IV load + infusion (Levy et al. 2018)

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C participants in the apixaban study who received andexanet, as a 400-mg intravenous bolus plus a 4-mg-per-minute infusion for 120 minutes, or placebo; and Panel D participants in the rivaroxaban study who received andexanet, as an 800-mg intravenous bolus plus a 8-mg-per-minute infusion for 120 minutes, or placebo. Different scales along the x axis in each graph are used to enable visualisation of the immediate, short-term dynamics as well as the longer-term dynamics of anti–factor Xa activity after andexanet treatment. The points on the graph represent the mean anti–factor Xa activity level, and I bars indicate the standard error. There was a significant difference ($P<0.05$) in the percent change in anti–factor Xa activity (relative to the pre-bolus activity level) between andexanet and placebo until 2 hours after administration of the bolus or infusion (Siegel et al. 2015).

As far as the use of prothrombin complex concentrates (PCC) is concerned, they have the potential to treat bleeding, but there is a lack of correlation between laboratory tests and bleeding or treat of anticoagulation. PCCs are used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation (Zahir et al. 2014; Dickneite et al. 2014; Heidbuchel et al. 2015; Levy et al. 2014; Weitz et al. 2015; Levi et al. 2014; Brown et al. 2016).

One of the most important things to remember is that bleeding and coagulopathy is a multi-modal defect that requires a multi-modal therapy. PCCs and other factor concentrates should be part of this multi-modal strategy.

With respect to managing bleeding with DOACs, some important factors to consider and certain important elements to remember:

- How urgent/emergent is the bleeding
- Whether there is time to decide if drug levels are contributing
- Whether the patient needs procedural intervention for the bleed
- Standard coagulation tests should be performed with bleeding and followed
- Reversal strategies are part of a multi-modal strategy in addition to fixing the bleeding lesion
- Reversal agents will only remove the role of the anticoagulant
- Identify and take out the source while minimising the amount of blood loss
- Critically ill patients require haemodynamic and haemostatic resuscitation

Finally, it is important to develop institution-wide protocols for emergencies. Also, it must be noted that reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at great risk for adverse outcomes (Crowther et al. 2016). ■

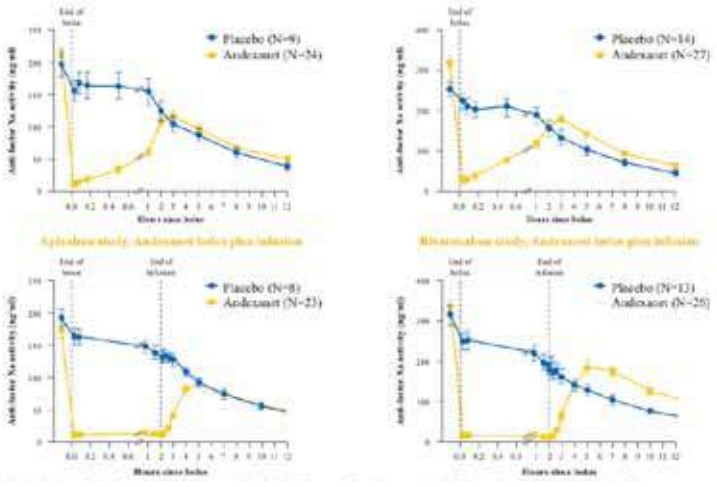

Figure 2. Time courses of anti–factor Xa activity before and after administration of andexanet (Siegel et al. 2015). Reprinted with permission from Massachusetts Medical Society

Key Points

- Managing bleeding is important, and developing a bleeding, and therapeutic plan is critical.
- Two of the state of the art reversal agents that can be used to manage a major bleed include idarucizumab and andexanet.
- PCCs can be used as part of an off-label multimodal approach with haemodynamic and haemostatic resuscitation.
- Reversal of anticoagulation does not always mean improved clinical outcomes because patients bleeding are already at greak risk for adverse outcomes.

Abbreviations

NOAC	non-vitamin K oral anticoagulants
DOAC	direct oral anticoagulants
INR	international normalised ratio
PCC	prothrombin complex concentrates
PT	prothrombin time
PTT	partial thromboplastin time

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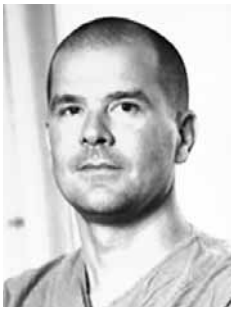
New ESPEN Guidelines for Nutrition in the Critically Ill: Help, What Happened!?



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ESPEN guidelines for nutrition in critical illness have shifted from optimistic anticipative nutritional pharmacotherapy towards cautious and balanced metabolic support. This important new orientation in ICU nutrition management is a consequence of recent strong RCT-based evidence.

Introduction

Recently, the new ESPEN guidelines for critically ill patients have been published. They are the result of two years of data collection, analysis, discussion, rewording, voting, and writing, under direction of Dr. Pierre Singer (Singer et al. 2018). The recommendations have shifted from early enhanced feeding towards more restricted feeding in the acute phase of critical illness. In this contribution we explain what provoked this major shift in the recommendations. We focus on how to interpret these new guidelines, distinguishing "should" from "can" and, likewise, "level A evidence" from "a strong agreement." High quality comparative clinical research of the last decade has resulted in steady progress towards novel, evidence-based nutrition management. Moreover, translational investigations within these trials have increased our understanding of the impact of nutritional management on recovery and functional outcome. These insights allow to design more individualised and dynamic time-adaptive feeding strategies, to be validated in future RCT's.

ESPEN GL for the ICU 2018: A Landslide in Nutrition Support for the Critically Ill

Table 1 summarises the major differences in recommendations between the ESPEN 2006 (Enteral Nutrition) and 2009 (Parenteral Nutrition) and 2018 (Nutrition) guidelines for the critically ill (Kreymann et al. 2006; Singer et al. 2009; Singer et al. 2018). A layman summary would be *"from optimistic anticipative nutritional pharmacotherapy towards cautious and balanced metabolic support."* Indeed, while the previous guidelines were built on preventing cumulative energy and protein debt and attenuating the inflammatory response to critical illness-induced stress, the recent guidelines focus primarily on avoiding iatrogenic harm. Initiation of PN is postponed, the energy target is lower in the acute phase, parenteral glutamine is abandoned, and the use of immune-modulating lipids is no longer recommended, but only suggested. More than ever, the importance of the refeeding syndrome is underscored.

How to Interpret the New ESPEN Guidelines for the Critically Ill?

The new ESPEN guidelines rely –wherever possible- on meta-analyses, conducted by a dedicated and independent epidemiologist, Rd. Waleed Alhazzani. The level A and level B evidence supported recommendations thus rely on statistically sound estimations of treatment effect.

Summarising the level A and B-evidence-supported recommendations, novel nutritional strategies are built on prioritising Enteral Nutrition (EN) rather than Parenteral Nutrition (PN), progressive (slow and titrated) build-up of nutrition doses and accepting hypocaloric feeding for up to 1 week if the gut doesn't tolerate more (Singer et al. 2018). The concept of nutrition as a drug, so-called pharmaconutrition, early in critical illness has been tested and was abandoned (Heyland et al. 2013; Manzanares et al. 2013).

For domains/topics where no reliable

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evidence was available yet, e.g. the optimal protein dose or feeding in patients with extremely low BMI (<17), the ESPEN-GL-panel aimed at providing some pragmatic guidance to clinicians. Such recommendations are worded in statements with "can" or "may" and level 0 evidence, leaving their implementation at the clinicians' discretion.

At the end of the data retrieval, analysis, and discussion process, the experts finally voted in favour or against every recommendation. The result of these votes is summarised as "strong consensus" (>90% agreement) or "consensus" (75-90% agreement). Importantly, strong consensus should not be confused with "strong recommendation." Indeed, strong consensus on a level zero recommendation "1.3 g/kg protein can be delivered" implies that the majority of the experts agreed that this might be a target but that the supporting evidence is extremely weak.

What Drove Experts to Write Guidelines So Different From the Previous Versions?!

For many ICU clinicians and nutritionists, these new guidelines may have been upsetting. Indeed, for many years, they have been striving to reach energy and protein targets early in critical illness. They might be wondering whether the current paradigm shift is just the pendulum of clinical guidelines and expert opinion swinging from the left to the right and back, from early –generous- to late –reluctant- nutritional support. The discrepancy between the older and new nutrition guidelines, however, are the consequence of a large body of novel strong evidence. Indeed, over the last decade, *approximately 20000 patients have been included in high-quality randomised controlled trials,* contributing to the generation of reliable clinical data. The lack of such data, unavoidably, resulted in the 2006 and 2009 guidelines, relying largely on physiological and epidemiological evidence. Indeed, numerous observational studies have associated an increased or optimal energy and protein delivery with an improved outcome. Such observations, however, are confounded by severity of illness. Indeed, it is easier to feed patients who are less severely ill. More generally, as SS Young and A Karr explain in a provocative and inspiring paper *"Any claim coming from an observational study is most likely to be wrong"* unless strict rules reducing bias of such analyses are applied (Young and Karr 2011).

Table 1. New evidence changing guidelines (Kreymann et al. 2006; Singer et al. 2009; Singer et al. 2018).

	ESPEN-2006/2009	ESPEN-2018
Time to initiate EN	Early EN (within 24h)	Early EN (within 48h)
Amount	Up to 25 kcal/kg over 2-3 days	Hypocaloric in the early phase; progressive increase until target within 3-7 days
Patients with shock	No contraindication for EN (monitor tolerance)	No EN in uncontrolled shock
In case of insufficient or contraindicated EN	Consider PN within 1-2 days	PN within 3-7 days
Glutamine	PN should contain glutamine	No parenteral glutamine

> "early enhanced feeding does not improve outcome and may evoke harm"

The recent Nutrition-RCTs are heterogeneous regarding their size and design, which increases the validity and generalisability of the aggregated data. Most large trials have been pragmatic, randomising thousands of patients to standardised feeding strategies (Arabi et al. 2015; Casaer et al. 2011; Chapman et al. 2018; Harvey et al. 2014; Reignier et al. 2018; Rice et al. 2012). Some smaller RCTs have elegantly provided labour-intensive titrated nutritional support, guided by indirect calorimetry and/or nitrogen balances (Allingstrup et al. 2017; Heidegger et al. 2013; Singer et al. 2011). All these different studies unanimously revealed that early enhanced feeding does not improve outcome and may evoke harm.

Hence, over the last years, metabolic support in critical illness has been enriched by the principles of modern comparative research and data aggregation, which generated novel and reliable guidelines, particularly regarding early nutrition management in critical illness.

These "Negative" RCTs on Nutrition - Aren't They All About Overfeeding? No

Several recent multicentre RCTs finding harm by early enhanced feeding have been criticised for having administered excessive energy and insufficient protein. Both the EPaNIC RCT in critically ill adults and the PEPaNIC RCT in critically ill children found prolonged ICU dependency by early PN supplementing insufficient EN, as compared to withholding supplemental PN until one week after ICU admission. In both RCTs, early PN evoked more infections and prolonged dependency on vital organ support (Casaer et al, 2011; Fivez et al 2016). In critically ill adults, early PN was also found to increase ICU-acquired muscle weakness and –in both children and adults- health care-related costs (van Puffelen et al. 2018b; Vanderheyden et al. 2012). Hence, both RCTs found that accepting a macronutrient deficit in patients with failing or contraindicated EN is superior

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to administering early PN. Pre-planned secondary analyses of both RCTs did not support the hypothesis that harm by early PN would be driven by excess energy intake (Mcclave et al. 2012; Casaer et al. 2013; Vanhorebeek et al. 2017). Indeed, in both EPaNIC and PEPaNIC, harm related to the administered amino acid dose, and not to the glucose and/or lipid dose.

A meta-analysis of studies comparing EN versus PN in critically ill patients suggested, however, that harm is evoked by the dose of nutrition given rather than the route (Elke et al. 2016). Indeed, Gunnar Elke and co-investigators revealed that PN in the first ICU week provoked more infections as compared to EN, but this was not the case for "isocaloric" studies providing EN and PN at comparable doses, such as the CALORIES and Nutritrea-2 trials (Harvey et al. 2014; Reignier et al. 2018). Likewise, RCTs evaluating supplemental PN tend to be neutral if the separation between nutrition doses in both arms was rather modest (Allingstrup et al. 2017; Heidegger et al. 2013). In none of the trials revealing harm by early up-to-target feeding, however, the energy or protein target was "excessive," considering the targets recommended at the time they have been conducted (Braunschweig et al. 2014; Casaer et al. 2011; Doig et al. 2015b; Singer et al. 2011). As a consequence, the beneficial effect in the control arm is more likely to be brought about by temporary nutrient restriction (Braunschweig et al. 2014; Casaer et al. 2011; Doig et al. 2015b). This is why the current guidelines recommend a more progressive (slower) build-up of energy provided (Singer et al. 2018).

Is Indirect Calorimetry the Solution to Prevent all These Nutrition-Related Complications? No

Indirect Calorimetry (IC) provides the best estimation of Resting Energy Expenditure, closest to Direct Calorimetry quantification of the amount of energy burned by a patient. IC is more accurate than equations based on biometrics and disease state (Reid 2007). ESPEN guidelines, thus, recommend relying on an indirect calorimeter when determining REE (level B Recommendation). Uncertainty remains, however, regarding how to apply measured REE in nutritional management. In the early phase of critical illness, the guidelines recommend keeping caloric intake below 70% of either measured or calculated REE (level B). The recommendation to target measured REE thereafter was graded "evidence level 0" reflecting the lack of evidence in support of IC-guided nutrition therapy. Indeed, Early Goal-Directed Nutrition (EGDN), initiated on ICU Day 1 and guided by IC and nitrogen balance did not improve functional outcome in the EAT-ICU trial (Allingstrup et al. 2017).

> "current guidelines recommend a more progressive (slower) build-up of energy provided"

Despite careful titration, EGDN actually increased ureagenesis and ICU length of stay. The TICACOS trial of early IC-guided PN revealed similar results (Singer et al. 2011), while the SPN trial evaluating later initiation of a low dose of IC-guided SPN together with EN revealed no impact on hard clinical endpoints (Heidegger et al. 2013). Importantly, in the PEPaNIC trial, Early-PN was equally detrimental in participating ICU's applying IC as in units relying on calculated REE (Fivez et al. 2016).

These discouraging results of IC early in critical illness may be explained by anabolic resistance. Indeed, in the acute phase of critical illness, nutrient mobilisation from endogenous reserves through catabolism is not suppressed by feeding (Schwarz et al. 2000). Hence, even when REE is measured very accurately, the nutrition provided comes "on-top" of this, increasing metabolic burden.

The impact of REE-guided nutrition therapy in prolonged critical illness may be more important, and deserves to be listed as a research priority. Nevertheless, even in expert hands, conducting repeated REE measurements in critical illness remains challenging and confounded by high FiO2, chest tubes, and continuous renal replacement therapy. This is reflected by the important proportion of study-patients in which no REE value could be obtained in recent RCTs (Heidegger et al. 2013).

Do all Patients Respond Equally to Nutritional Interventions?

Obviously, ICU patients are a very heterogeneous population including well-nourished patients admitted after major surgery and chronically underfed patients treated for sepsis. Pre-planned subgroup analyses in some of the larger RCTs determined whether patients respond differently to enhanced nutrition interventions (Arabi et al. 2016; Casaer et al. 2011; Fivez et al. 2016). In summary, no differential response was detected in patients with or without sepsis, medical versus surgical patients, different BMI categories or high versus low nutritional risk scores. Also in critically ill children, patients deemed to be at the highest nutritional risk (neonates and patients with a high nutritional risk score) were significantly harmed by early supplemental PN (Fivez et al. 2016; van Puffelen et al. 2018a; van Puffelen et al. 2018c). Finally, in the pilot TOP-UP RCT, early PN had no benefit when provided only to patients presumed to be at high nutritional risk (Wischmeyer et al. 2017).

The differential effect of temporary nutrient restriction on long-term rehabilitation as compared to acute outcomes is another common concern. However, in none of the trials studying long-term functional outcome, lower protein and/or energy intake had any untoward effect

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(Allingstrup et al. 2017; Doig et al. 2015a; Needham et al. 2013). Moreover, in the EPaNIC RCT, early PN actually increased weakness, and hampered recovery thereof. Mechanistic studies have implicated feeding-induced suppression of autophagy, a crucial cellular recovery process, as a culprit (Hermans et al. 2013). In the PEPaNIC RCT, finally, Early-PN compromised neurocognitive development, as assessed 2 years after randomisation (Verstraete et al. 2019).

The Time-to-Start-Feeding Indicator

The 2018 version of the ESPEN GL recommends waiting 3 to 7 days before initiating PN when EN fails and before increasing energy intake up to target (Singer et al. 2018), which highlights the remaining uncertainty on how long caloric restriction can be tolerated. Even the 7-day cut-off may not be strict since a more prolonged nutrient restriction has never been studied. The ideal time when patients do benefit from artificial nutrition may vary, and may depend on the severity of illness and its evolution over time. A more individualised determination of when a patient may benefit or at least not experience harm from enhanced nutrition support would be very welcome. A reliable real-time indicator of the organism converting to anabolism is yet to be identified. Such insights may be helpful in designing a "ready-to-feed" monitor and a novel dynamic feeding strategy, to be evaluated in future RCTs.

Conclusion

Recent RCTs in ICU have allowed to design evidence-based nutrition strategies for the acute critically ill. Since none of the available nutritional risk parameters identified patients benefiting from early or enhanced feeding, most recent feeding guidelines promoting hypocaloric feeding in the acute phase of critical illness can be applied to all ICU-patients. Future research, particularly focusing on the post-acute and prolonged critically ill patients and identifying the time of anabolic switch would allow to further improve patient care.

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Abbreviations

BMI	Body Mass Index
EGDN	Early Goal Directed Nutrition
EN	Enteral Nutrition
ESPEN	European Society of Parenteral and Enteral Nutrition
IC	Indirect Calorimetry
ICU	Intensive Care Unit
PN	Parenteral Nutrition
RCT	Randomised Controlled Trial
REE	Resting Energy Expenditure

Key points

- Novel nutritional strategies are built on prioritising enteral nutrition rather than parenteral nutrition, progressive build-up of nutrition doses and accepting hypocaloric feeding for up to 1 week.
- Over the last years, metabolic support in critical illness has been enriched by the principles of modern comparative research and data aggregation, which generated novel and reliable guidelines.
- Recent feeding guidelines promoting hypocaloric feeding in the acute phase of critical illness can be applied to all ICU-patients.

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[1] Castillo et al. *Acta Paediatr*. 2011 Feb;100(2):188-92. [2] Zhao et al. *Lancet* 2014 Aug 30;384(9945):747-54. [3] Taenzer AH et al. *Anesthesiology*. 2010:112(2):282-287.

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New Trends in ICU Nutrition

The new trends in nutrition management included in the last guidelines are discussed, in particular the route and the dose of calories and proteins recommended.

During the last decade, numerous paradigms and dogmas based on observational cohort studies were challenged by the publication of large multicentre prospective randomised controlled trials (RCT). Actually, until recently, the guidelines were supported by a very low evidence and were frequently expert opinions, implying controversial recommendations (Patel et al. 2017; McCarthy et al. 2016; Preiser et al, 2015). The very recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (Singer et al. 2019) take into account the latest RCT and updated expert opinion. Its content is really useful for the bedside caregiver. Two other publications deserve also a mention as they could help to guide the practical bedside daily nutrition management (Berger et al. 2019; Reintam Blaser et al. 2017). We will briefly focus on the main new principles underlying the nutritional management of a critically ill patient.

Who Should be Nourished?

All the patients admitted to the ICU (Intensive Care Unit) and staying more than 48h are at nutritional risk and deserve particular attention. The general assessment does not differ from any other hospitalised patient (Singer et al. 2019).

When and How?

The gut should be used if available by oral or enteral route. The oral route is commonly used (Bendavid et al. 2017). So, careful monitoring of the oral intake could permit to detect patients who will benefit from early (within 48h) enteral nutrition. Despite the absence of clear differences between short-term early enteral route and early parenteral route in recent RCTs (Harvey et al. 2014; Reignier et al. 2018), the former route is still recommended when there is no contraindication. The arguments are mainly the maintenance of the intestinal barrier integrity by the EN (trophic feeding) and its low cost. The list of contraindications to the enteral route decreased year by year and the ESICM (European Society of Intensive Care Medicine) clinical practice guidelines formulated 17 recommendations for specific conditions (Reintam-Blaser et al. 2017). They were endorsed by the ESPEN Guidelines and they more clearly defined the situation necessitating a careful usage of the enteral route (**Table 1**) (Singer et al. 2019).

> **recent ESPEN guidelines take into account the latest RCT and updated expert opinion**

When the enteral route is not available, a parenteral nutrition (PN) should be implemented at a later stage, before the seventh day after admission. The importance of permissive underfeeding to avoid overfeeding during the acute phase (3-7 days) is emphasised (Reintam-Blaser and Berger 2017) and a full feeding (i.e. calculated to match energy expenditure (EE) and protein losses) was discouraged during the first days (Singer et al. 2019; Preiser and Wernerman 2017). A progressive increase of the intake is then recommended.

Historically, numerous observational studies showed that a low caloric and protein intake is associated with poor outcomes (Alberda et al. 2009; Villet et al. 2005). However interventional studies failed to demonstrate that increasing the caloric intake to the level of EE measured or predicted improved the outcome (Rice et al. 2011; Allingstrup et al. 2017; Arabi et al. 2015; Peake et al. 2014). As the enteral route could be insufficient to reach this target, the parenteral route (supplemental) was tested (Heidegger et al. 2013; Singer et al. 2011; Casaer et al. 2011; Harvey et al. 2014; Doig et al. 2013). However, the results did not show any consistent improvements in the mortality or the morbidity of the critically ill patients and even suggest that early full intake is deleterious (Zusman et al. 2016). The actual recommendation is to administer hypocaloric nutrition (not more than 70% of EE) during the early phase of acute illness and to increase the caloric delivery after day 3 up to 80-100% of measured EE if a reliable method of measurement is used (Singer et al. 2019). The indirect

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calorimetry is nowadays the sole reliable method available but is not widely accessible (Rattanachaiwong and Singer 2019). The alternative method, the predictive equations were clearly unreliable leading to individual unpredictable underfeeding or overfeeding. This justifies the preferred use of hypocaloric nutrition over isocaloric nutrition for the first week of ICU stay when these equations were used (Singer et al. 2019).

The gold standard indirect calorimeter was not sold since more than 20 years and the devices manufactured during the last decades were known to be unreliable (Fraipont and Preiser 2013). A group of experts sponsored by the ESICM and the ESPEN worked in collaboration with the industry to conceive a new tool without the inconvenience of the older ones (Oshima et al. 2017a). This apparatus was released last year and promises to be useful. It is light, easily mobilised, with easy calibration process, equipped with a friendly touch screen and interface, easy to use and seems to be reliable in in-vitro mass spectrometry validation studies (Oshima et al. 2017b).

The management of difficult EN achievement is not different from the past and call on prokinetics and lastly post-pyloric route. When the prescribed dose of EN is not reached after one week, a supplemental PN should be considered on a case by case basis (Singer et al. 2019).

Recent interests emerged and focused on the possible role of an increased protein intake (Preiser, 2018; Weijs 2018); however very few controlled data were available (Rugeles et al, 2013; Fetterplace et al. 2018; Allingstrup et al. 2017) and some warnings signs emerged from retrospective analysis (Casaer et al. 2013; Koekkoek et al. 2019). Therefore, the dose of protein recommended is 1.3 g/kg protein equivalents per day in opposite with the more generous guidelines of the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (McClave et al. 2016).

Pharmaconutriments

Additional enteral doses of glutamine are limited to patients with burns > 20% body surface area or critically ill trauma. In case of unstable or complex ICU patients with hepatic or renal failure, intravenous supplements are also not recommended. The use of enteral omega-3 fatty acids is limited to nutritional doses. High doses of antioxidants is also not recommended but micronutriments (trace elements and vitamins) should be provided at the daily recommended dosage if the patient is under exclusive PN or if he did not receive sufficient EN (Singer et al. 2019). For the first time, following the result of a recent interventional study (Amrein et al. 2014), the guidelines pay attention to vitamin D recommending its dosage and supplementation with high doses in case of severe deficiency (Singer et al. 2019).

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Table 1. Category of specific patients that could be candidate to EN (grade of recommendation: B – strong consensus). Adapted from Singer et al. Clin. Nutr. 2019;38:48-79.

Low dose EN should be administered
☐ in patients receiving therapeutic hypothermia and increasing the dose after rewarming;
☐ in patients with intra-abdominal hypertension without abdominal compartment syndrome, whereas temporary reduction or discontinuation of EN should be considered when intra-abdominal pressure values further increase under EN; and
☐ in patients with acute liver failure when acute, immediately life-threatening metabolic derangements are controlled with or without liver support strategies, independent on grade of encephalopathy.
Early EN can be performed
☐ in patients receiving ECMO
☐ in patients with traumatic brain injury
☐ in patients with stroke (ischaemic or haemorrhagic)
☐ in patients with spinal cord injury
☐ in patients with severe acute pancreatitis
☐ in patients after GI surgery
☐ in patients after abdominal aortic surgery
☐ in patients with abdominal trauma when the continuity of the GI tract is confirmed/ restored
☐ in patients receiving neuromuscular blocking agents
☐ in patients managed in prone position
☐ in patients with open abdomen
☐ regardless of the presence of bowel sounds unless bowel ischaemia or obstruction is suspected in patients with diarrhoea

Specific Conditions

The importance of detecting dysphagia that could limit the oral intake is underlined as this dysfunction is very frequent in the critically ill patients (Zuercher et al. 2019). Following the publication of a large study on early EN versus early PN in ventilated adults with shock (Reignier et al. 2018) that showed possible harmful with the enteral route, the statement is that early and progressive EN should be used in septic patients after haemodynamic stabilisation (Singer et al. 2019). Early EN was also suggested in patients that were classically not good candidates for EN (**Table 1**) (Singer et al. 2019).

As the proportion of obese patients increases in most of the countries (Schetz et al. 2019), this setting is discussed in the ESPEN guidelines. The energy intake should be guided by indirect calorimetry and an iso-caloric high protein diet can be administered even if the grade of recommendation is low (Singer et al. 2019).

> **indirect calorimetry is nowadays the sole reliable method available but is not widely accessible**

Close monitoring of the blood glucose and electrolytes is still the rule. A particular focus is made on the detection and management of the refeeding syndrome. Indeed, a large RCT showed that restricted energy supply during 48h followed by progressive increase in patient with refeeding hypophosphataemia (< 0.65 µmol/l or a drop of > 0.16 µmol/l) saves life (Doig et al. 2015).

Future

A great number of recommendations were not based on high evidence and a group of experts published (Arabi et al. 2017) a research agenda in nutrition and metabolism to be done in the next 10 years. We hope that these future researches will provide clearer pragmatic attitudes for the practitioner involved in nutritional management. ■

Conflicts of Interest

None

Abbreviations

EE	energy expenditure
EN	enteral nutrition
ESICM	European Society of Intensive Care Medicine
ESPEN	European Society for Clinical Nutrition and Metabolism
ICU	intensive care unit
PN	parenteral nutrition
RCT	randomised controlled trials

Key points

- Patients admitted to the ICU and staying more than 48h are at nutritional risk and deserve particular attention.
- Enteral route is still recommended when there is no contraindication.
- When the enteral route is not available, a parenteral nutrition should be implemented at a later stage.
- Hypocaloric nutrition is preferred over isocaloric nutrition for the first week of ICU stay.
- A new indirect calorimeter that is light, easily mobillised, with easy calibration process, equipped with a friendly touch screen and interface and that is reliable was recently released.

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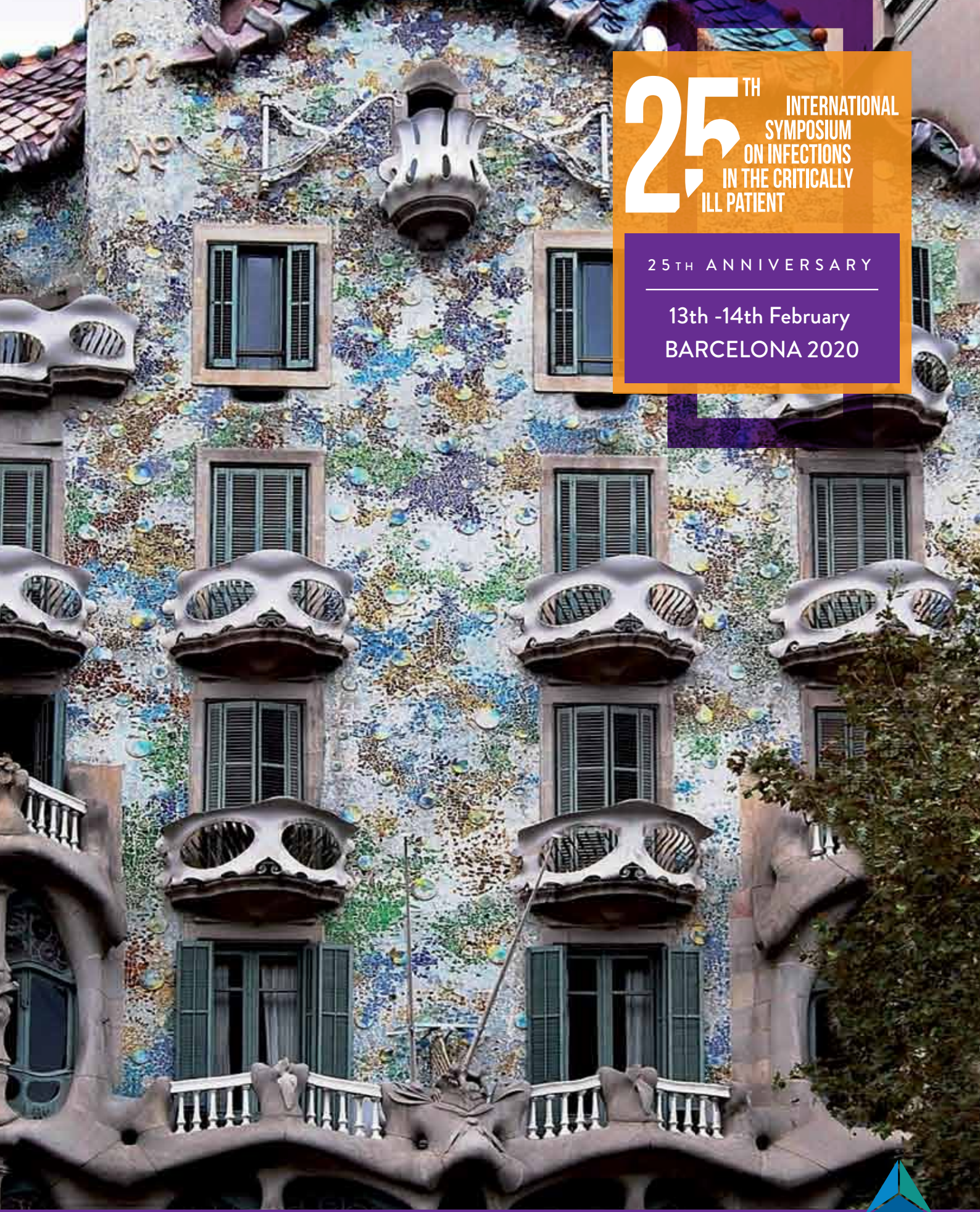

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Addressing Malnutrition in Critically Ill Patients

Baxter launches a new parenteral nutrition formulation designed to meet the need for higher protein provision in Europe and signs a global partnership with COSMED to commercialise Q-NRG+, a metabolic monitoring device that utilises indirect calorimetry technology.

Malnutrition in the ICU

Around 20 to 50% of hospital patients, including those in the ICU (trauma, surgery) are malnourished.[1] Malnutrition is a clinical condition that affects multiple patient groups and can have a significant impact on both clinical outcomes and healthcare systems, as it is typically associated with higher infection rates, increased morbidity and mortality, longer hospital stays, increased healthcare costs and reduced quality of life.

Critical illness often results in rapid protein breakdown and muscle loss. Clinical evidence shows that nutrition that involves both moderate energy intake and high protein is associated with reduced mortality. Both the European Society of Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommend a higher protein intake with controlled calorie for critically ill patients.[2 3]

Clinical Nutrition Innovations

Clinical nutrition in the ICU has evolved over the years. Baxter International Inc., a global leader in clinical nutrition, has been a part of this journey, listening to clinicians and addressing the unmet needs in the critical care segment in line with nutritional guidelines that have moved towards acknowledging the importance of meeting protein targets in critically ill patients. Baxter have recently launched a number of innovations that will enable clinicians to identify and address malnutrition in the critically ill. Along with COSMED, a worldwide leader in the design of metabolic systems for clinical and human performance application, Baxter will be commercialising Q-NRG+; a metabolic monitoring device that utilises indirect calorimetry technology, in 18 key countries around the world with potential for future expansion.

Indirect calorimetry (IC) is the gold standard[4] for measuring resting energy expenditure (REE) - a patient's calorie needs while at rest. The ESPEN guidelines recommend that in critically ill mechanically ventilated patients, energy needs should be determined using indirect calorimetry.[2] The ASPEN guidelines also suggest that IC be used to determine energy requirements, and in the absence of IC, a predictive equation or a weight-based equation be used.[3]

Q-NRG+ represents the next generation of IC technology and enables individualised monitoring measurements to help clinicians optimise nutrition therapy in critically ill patients. Q-NRG+ is designed to address barriers to rapidly and accurately measure a patient's REE.[5] It is flexible, portable, and easy to use by all clinicians. The device requires minimal warm-up and calibration time and can deliver readings in as few as five minutes.

Q-NRG+ is a unique product that is a result of collaboration with world-class institutes in the field of nutrition support in ICUs. It is simple to use and can solve typical pitfalls of previous IC technology. With Q-NRG+, clinicians will now have access to an effective and practical tool that can be used at the point of care.

Baxter have also launched in Europe,

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their latest addition to their olive oil-based parenteral nutrition (PN) triple chamber bag portfolio; Olimel N12. The new PN bag combines a high protein formulation with low glucose content, resulting in the lowest energy to protein ratio currently available in a standardised, triple-chamber bag. The new formulation contains 76g of amino acid per liter (designed to meet protein targets in lower fluid volumes) and only 73g of glucose per liter (helping to reduce the potential glycaemic load and subsequent risk of hyperglycaemia). The olive-oil based lipid emulsion may preserve immune function.[6 7 8 9 10]

Future Outlook

As clinical nutrition continues to gain importance in the ICU setting, the need for advanced strategies and tools that could help clinicians ensure patients receive adequate nutrition for better long-term outcomes and improved quality of life will be fundamental. Baxter is committed in its role as a leader in clinical nutrition and continues to partner with institutions and clinicians to develop innovations that will improve outcomes for critically ill patients. ■

* IMPORTANT SAFETY/ RISK INFORMATION FOR OLIMEL N12

Therapeutic indications:
PERIOLIMEL/OLIMEL are indicated for parenteral nutrition for adults and children greater than 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

PERIOLIMEL/OLIMEL are not recommended for use in children less than 2 years of age due to inadequate composition and volume.

Contraindications:
The use of PERIOLIMEL/OLIMEL with and without electrolytes are contra-indicated in the following situations:

- In premature neonates, infants and children less than 2 years of age
- Hypersensitivity to egg, soybean, or peanut proteins, or to any of the active substances or excipients
- Congenital abnormalities of amino acid metabolism
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterised by hypertriglyceridaemia
- Severe hyperglycaemia

The use of PERIOLIMEL/OLIMEL with electrolytes are contra-indicated in the following situations:

- Pathologically-elevated plasma concentrations of sodium, potassium, magnesium, calcium, and/or phosphorus.

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Q-NRG is a registered trademark of COSMED.

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Emerging Concepts in Nutritional Therapy for the Critically Ill Child

Prudent strategies to optimise nutrition during critical illness, with the aim of improving long-term outcomes, avoiding loss of muscle mass and function, and preserving quality of life.

Introduction

Optimal delivery of nutrients to the critically ill patient might prevent nutritional deterioration and expedite recovery. Prospective cohort studies have demonstrated the independent association between nutritional status and important clinical outcomes (de Souza Menezes et al. 2012). Furthermore, failure to provide adequate nutrient intake during critical illness has been associated with deterioration of nutritional status and poor clinical outcomes (Mehta et al. 2012; Mehta et al. 2015). Hence, optimal nutrition therapy is an important component of the care of critically ill children and an area of ongoing interest and inquiry. The impact of specific nutrition strategies on clinical outcomes have not been adequately demonstrated in randomised clinical trials. As a result, there is some uncertainty about the optimal timing, route and dose of nutrition therapy during critical illness, and practice patterns at the bedside vary widely across PICUs worldwide. This era of increased interest but scant evidence is fertile for myths and dogma arising from observational studies, poorly designed trials with limited external validity, and expert opinion. A basic understanding of the metabolic demands from critical illness might help develop a sound nutrition strategy. **Figure 1** depicts the key aspects of the metabolic stress response to critical illness in humans (Mehta and Jaksic 2008). The energy burden and protein loss that are imposed by this response are relevant targets that may be addressed by optimal delivery of these macronutrients to support the individual and prevent lean body mass loss during critical illness. Investigations over past decades have highlighted that energy requirements may be lower than expected, and the energy expenditure estimations by standard equations are inaccurate, often leading to overfeeding.

> "the nutrition prescription in critically ill children must be individualised for each patient avoiding overfeeding"

Protein breakdown is the principal feature of the stress response to critical illness and may result in lean body mass loss that is undesirable. Optimal energy and protein delivery, while preventing overfeeding, may help offset protein losses and preserve muscle mass and long-term function in critically ill patients.

Nutrition Therapy – Key Questions

There are 3 fundamental questions related to nutrition during acute critical illness:

- What is the optimal dose for macronutrients (energy, protein) and the role for supplemental micronutrients?
- What is the best route for nutrient delivery: a) enteral nutrition - EN; b) parenteral nutrition - PN; or c) EN with supplemental PN.
- What is the best timing for EN initiation and when (early vs. late) should PN be initiated as a supplement if EN is not feasible or insufficient?

Optimal nutrition therapy involves careful prescription of the dose of energy, protein and micronutrients; delivered at appropriate time during the illness course; via the most appropriate and safe route. These decisions are often interlinked and the optimal strategy may vary between individuals, dependent on the nature and severity of illness and its metabolic effects, nutritional status and gastrointestinal dysfunction. Unfortunately, the few trials that do exist on this subject have explored a one size fits all strategy applied uniformly to a vastly heterogeneous patient population. Some of the trials have limited external validity and practical questions related to bedside practice during critical illness remain unanswered. The optimal design that allows careful examination of these interrelated concepts remains elusive. While some of these questions will require rigorous examination by randomised allocation of distinct therapies; the quest to determine one uniform strategy that would apply to all PICU patients is quixotic and

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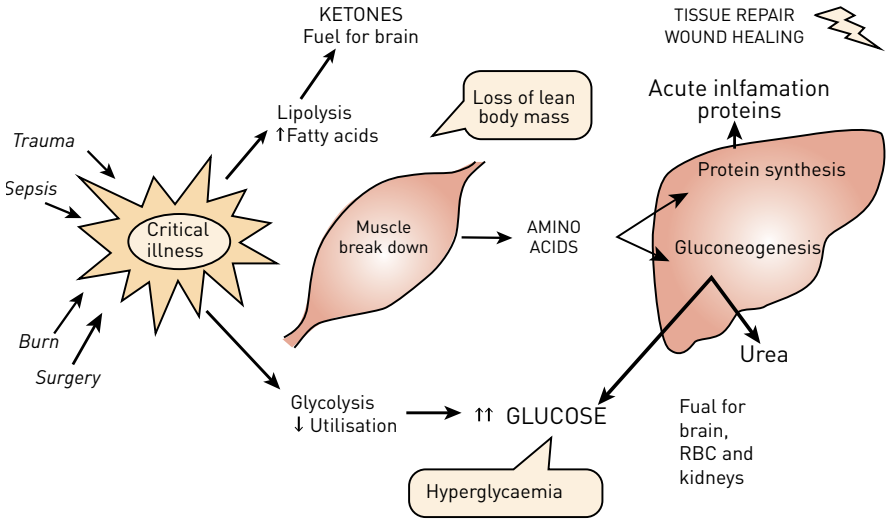

Figure 1. The stress response to critical illness – protein breakdown. Source: Mehta and Jaksic 2008.

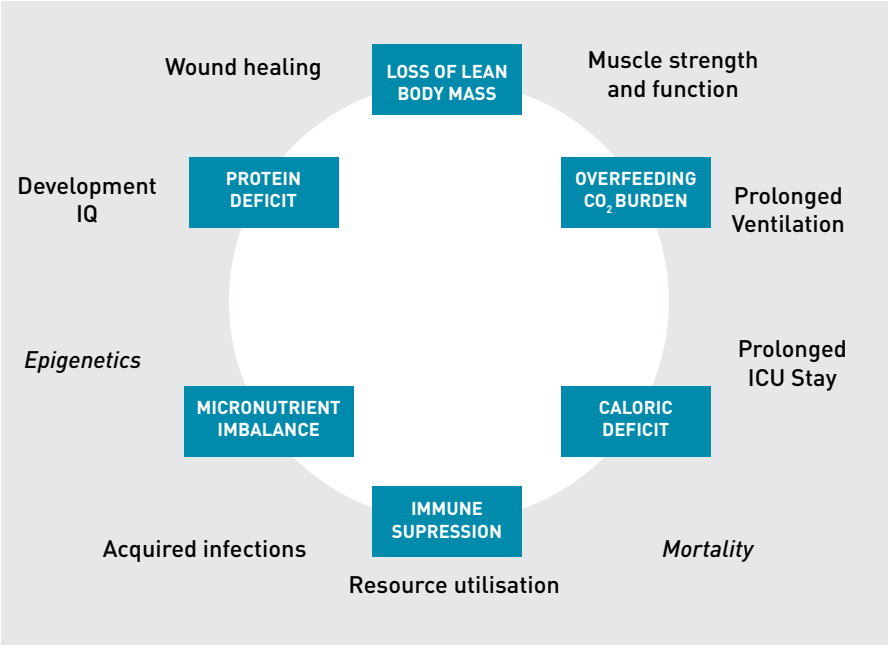

Figure 2. Outcomes for critical care nutrition trials – call for uniform data elements

must be abandoned. Future trials must employ innovative and more meaningful study designs to account for the interplay between dose, route and timing of nutrient delivery. These trials must include relevant clinical outcomes, and a core set of well-defined data elements must be employed to allow results from different trials to be compared. There are ongoing efforts to develop such a core set that include meaningful outcomes beyond survival.

Figure 2 shows the common surrogate and functional outcomes of interest for future nutritional trials. Preservation of muscle mass and function is the most important short-term outcome that may be associated with improved functional and clinical outcomes from critical illness. The role of nutrition along with other non-nutritional strategies in preserving muscle mass and function is therefore an area of ongoing investigation.

Evaluating Emerging Evidence for Nutrition Therapy – Guidelines

Individual practitioners must carefully assess the merits and validity of each emerging study and determine the applicability of its results to their patients. Randomised controlled trials (RCT) are recognised as the strongest clinical evidence, however weaknesses in the design or implementation of an RCT will decrease the quality of that evidence. Furthermore, single trials are often refuted in clinical medicine and premature adoption of practices based on limited evidence should be avoided. Due to the scarcity of robust RCTs, a majority of nutritional practices in the PICU have been adopted based on observational data from cohort studies or expert opinion. Regular review of the literature and translation of the cumulative evidence into practical recommendations is essential. There have been significant advances in the process of systematic assessment and cumulative incorporation of emerging trial results into guidelines. The GRADE methodology for review of literature is used to develop best practice recommendations and is described in **Table 1** (Druyan et al. 2012; Guyatt et al. 2008).

The American Society for Parenteral & Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) have recently published an exhaustive review of evidence and generation of evidence tables that were then translated by a multidisciplinary group of experts into practice recommendations for nutrition therapy in the paediatric intensive care unit (Mehta et al. 2017). These guidelines must be revised and updated every few years to reflect emerging evidence. **Table 2** summarises key recommendations from these guidelines.

A Pragmatic Approach to Nutrition in the PICU

Step 1: Nutrition Prescription

Nutrition screening helps identify patients who are at a high risk of nutritional deterioration and poor outcome; it allows

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Table 1A. GRADE methodology – the quality of evidence and definitions. Adapted from Guyatt et al. for the GRADE Working Group.

Quality	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate
Very low	Any estimate of effect is very uncertain

Table 1B. GRADE criteria for grading evidence.

Type of Evidence	Initial Grade	Criteria to Decrease Grade	Criteria to Increase Grade	Final Quality Grade
RCT	High	Study Limitations Serious (-1) or very serious (-2) limitation to study quality Consistency Important inconsistency (-1) Directions Some (-1) or major (-2) uncertainty about directions Precision Imprecise or sparse data (-1) Publication bias High probability of reporting bias (1)	Strong Association Strong evidence of association - significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1). Very strong evidence of association - significant relative risk of >5 (<0.2) based on direct evidence with no major treats to validity (+2) Dose response gradient Evidence of a dose response gradient (+1) Unmeasured Confounders All plausible confounders would have reduced the effect (+1)	High Moderate Low Very Low
OBS	Low			
Expert Opinion	Low			Very Low

OBS, observational study; RCT, randomised controlled trial

early allocation of limited nutritional resources where they might have the most impact. However, a valid screen for critically ill children is not available. Detailed nutritional assessment allows detection of existing nutritional deficiencies and specific disease related nutritional needs. Energy requirement may be highly variable and based on the nature of illness/injury. Indirect calorimetry (IC), during steady-state conditions, is the gold standard method for accurate energy expenditure assessment (Mehta et al. 2017). However, IC may not be feasible in a large subset of children due to technological and physiologic hurdles. When IC is not feasible or available, estimates of energy expenditure using standard equations plus stress factors to adjust for illness severity and activity have been used to guide energy prescription. However, equation estimates are inaccurate and may result in unintended underfeeding or overfeeding of energy, which may impact patient outcomes (White et al. 2000; Ladd et al. 2018). These equations were developed in populations of healthy children and therefore may not reflect energy expenditure in critically ill children. Sedated and mechanically ventilated children, in thermoneutral environments in modern ICUs, may have significant reduction in energy expenditure. These patients may be at a risk of overfeeding when prescriptions are guided by estimates of energy requirements, especially if stress factors are incorporated (**Figure 3**). In the absence of IC, Schofield/WHO equations may be used as a guide (Mehta et al. 2017). Stress or correction factors should only be applied after careful consideration of metabolic status in individual cases. In a large cohort study, delivery of 2/3 of the prescribed amount was associated with improved outcomes. Hence, guidelines recommend 2/3 (rather than full) prescription as appropriate target for energy delivery in the first week of critical illness.

Large observational study data have shown strong association between increased protein delivery (percentage of the prescribed target) and lower 28-day mortality. Previous trials have also shown that protein supplementation increases the likelihood of achieving a positive protein balance (Mehta et al. 2015). However, the optimal dose of protein that is associated with improved clinical outcomes has not been studied using randomised controlled trials. Furthermore, the secondary analysis from a recent RCT examining timing of PN, implicated amino acids as the macronutrient responsible for the adverse effects of an aggressive approach to early initiation of PN (Fivez et al. 2016). Therefore, a well-designed dosing study of protein in the first week of critical illness is desirable.

Overall, the nutrition prescription in critically ill children must be individualised for each patient. The energy dose should

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Table 2. SCCM + ASPEN guidelines for nutrition therapy for the critically ill child. Source: Mehta et al. 2017

Topic	Recommendation	Evidence	GRADE	Future studies
Nutrition status and outcomes	Malnutrition, including obesity, is associated with poor outcomes	Very low	Strong	Definition of malnutrition
Nutrition screening	Obtain accurate anthropometry on admission and serially; use Z-score cut-offs. Patients should be screened within 48 hours of admission to detect those at high risk of nutritional deterioration and poor clinical outcomes	Very low	Strong	A valid screen for PICU patients is currently not available.
Energy requirement and delivery	Measured energy expenditure (using Indirect Calorimetry) is preferred as a guide to energy prescription. Equations are often inaccurate, but if IC not available, then use Schofield/ WHO equation (without stress factors) as initial guide. Deliver at least two-thirds of the prescribed daily energy requirement by the end of the first week in the PICU	Low Very low	Weak Weak	IC directed energy prescription has not been shown to improve clinical outcomes in trials. The route of delivery and dose of nutrients are linked - careful examination of these aspects in future trials is desirable.
Protein requirement and delivery	Minimum daily protein intake of 1.5g/kg. Do not recommend RDA values to guide prescription. Protein should be delivered early and via the enteral route.	Moderate Moderate	Strong Weak	Dosing trials that show impact on clinical outcomes are lacking The route of delivery and dose of nutrients are linked - careful examination of these aspects in future trials is desirable.
Route of nutrition delivery – Enteral	EN is feasible and the preferred mode of nutrient delivery. May improve GI motility and mucosal integrity. Trophic feeding may be initiated within 24-48 hours of admission, if patient is stable, and advanced at optimal rate using a stepwise algorithm that helps manage intolerance. Be aware of barriers, including avoidable interruptions, to EN. Gastric feeding is preferred. Postpyloric site, if feasible, may be used in select patients with intolerance to gastric feeds.	Low Low	Strong Weak	The merits of a continuous versus intermittent feeding strategy needs further study. Role of gastric residual volume (GRV) as a guide to EN intolerance is questionable and requires further study.
Route of nutrition delivery - Parenteral	Do not recommend using PN within 24 hours of admission. PN to be reserved for patients with contraindications to EN or in those where EN is insufficient (supplemental). Timing of supplemental PN must be individualised and may be deferred in the first week if nutritional status is adequate. May consider earlier in newborns or those with severe malnutrition on admission.	Moderate Low	Strong Weak	Trials that account for the interrelation between the timing of PN and dose are required. The role of supplemental PN after the first 24 hrs in the PICU needs further examination.
Immunonutrition	Not recommended	Moderate	Strong	

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preferably be guided by measurements of energy expenditure. Optimal protein dosing and timing are recently being questioned, although most observational and trials data suggest that a minimal protein intake of 1.5g/kg/day is associated with improved outcomes (Mehta et al. 2017).

Step 2: Optimal Nutrition Delivery – Enteral Route

Enteral nutrition is preferred and is feasible in a majority of critically ill children. Small volume, nonnutritive, feeding in the gut has benefits and may be initiated within 24-48 hours of admission in children with a functioning gastrointestinal tract, initiated soon after haemodynamic stabilisation. Stepwise protocols have been shown to optimise advancement of EN, guiding rates of feeding and assisting in the diagnosis and management of EN intolerance. **Figure 4** shows an example of a stepwise EN advancement protocol (Hamilton et al. 2014). Interruptions for procedures, intolerance to EN and fluid restriction are common barriers to achieving goal nutrient delivery via the enteral route. Attention to these barriers in the ICU and efforts to decrease, when possible, fasting times in critically ill children are desirable (Mehta et al. 2010). EN intolerance remains challenging as we update our definition and management strategies. Elevated gastric residual volume (GRV) is routinely used in a majority of ICUs as a surrogate for intolerance. However, this practice of stopping feeds based on a threshold GRV value has been challenged and it may not be used as a singular marker of EN intolerance (Tume et al. 2017). Improving our understanding of the mechanisms of gastrointestinal dysmotility during critical illness and developing strategies to ameliorate it are desirable. Overall, we have made significant strides in achieving safe and optimal delivery of enteral nutrition in the critically ill child, and strategies for optimising EN remain an area of great interest and ongoing investigation in critical care.

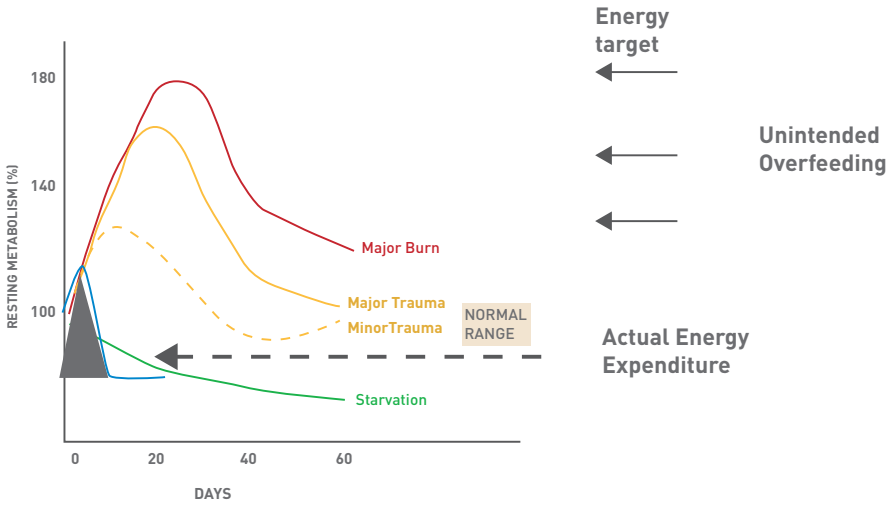

Figure 3. Energy targets and the potential for overfeeding during critical illness

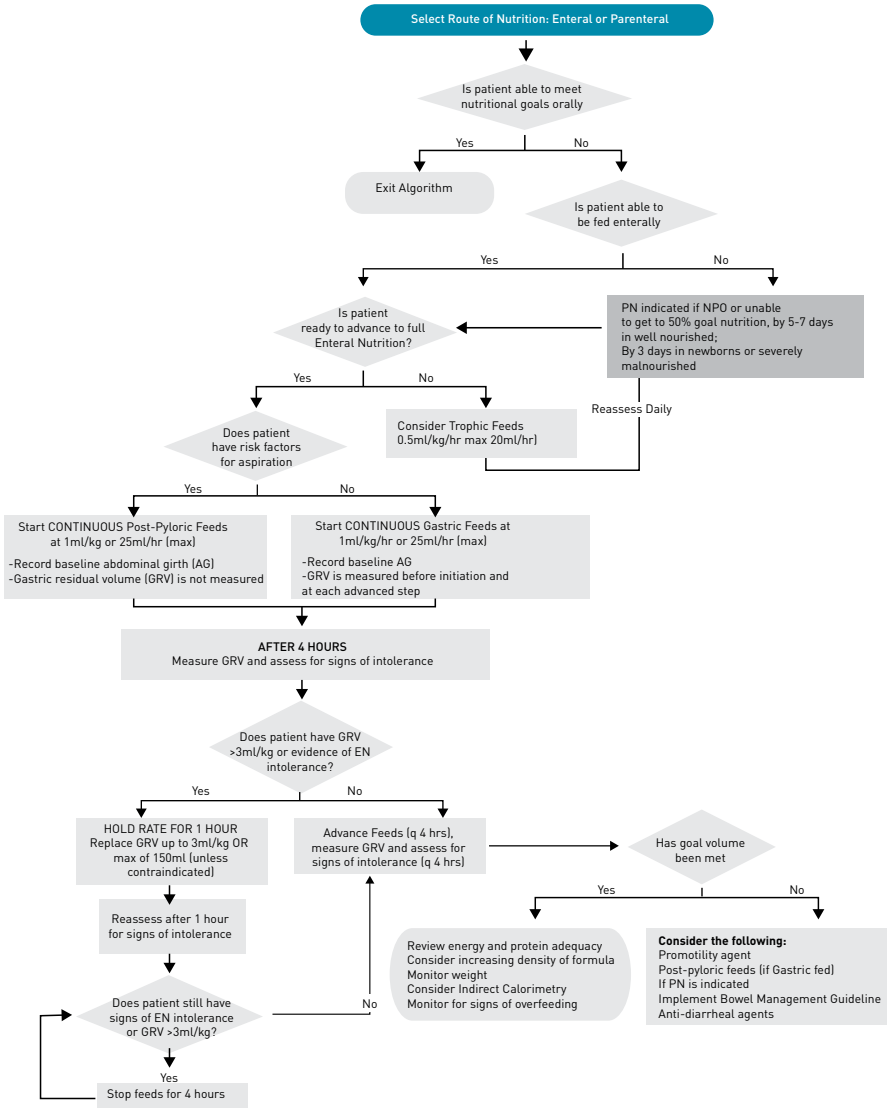

Figure 4. Stepwise EN algorithm. Source: Hamilton et al. 2014.

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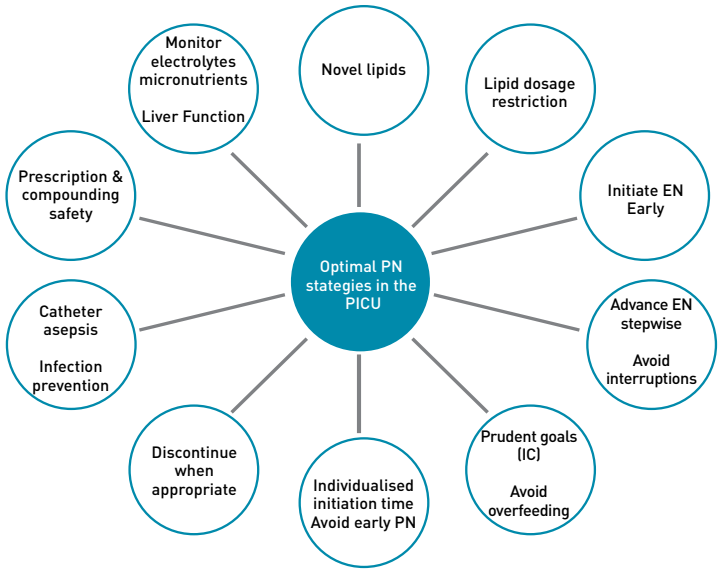

Figure 5. Strategies for safe and optimal use of PN

Step 3: Optimal Nutrition Delivery – Parenteral Route

However, in many patients, EN is either contraindicated, not tolerated, and therefore insufficient to meet the nutritional needs alone. Parenteral nutrition (PN) emerged in the 20th century as a life-saving therapy in such circumstances (Wilmore et al. 1968). Over the years, attention to PN safety and prudent PN strategies have allowed us to utilise the benefits of this mode of nutrition delivery, while balancing against its potential complications. Central catheter associated blood stream infection and PN associated cholestasis and liver disease are important considerations in children dependent on PN. Therefore, the timing of PN as a supplemental nutrition delivery mode has been an area of controversy and investigation in adult and paediatric critical care. In a recent randomised controlled trial, an aggressive early PN approach (initiated within 24 hours of admission to the PICU) was shown to be associated with longer PICU stay and increased likelihood of acquired infections, compared to a late PN strategy (initiated after 7 days) (Fivez et al. 2016). Despite the debate surrounding the study design and its external validity, it clearly demonstrated that PN use soon after admission to the PICU is not beneficial as a uniform strategy, and in most cases PN may be deferred during the first week in the PICU, while providing adequate micronutrients and advancing EN as tolerated. In particular, the ill effects of the early PN strategy may also be related to the potential overfeeding in this group, compared to those that were randomised to the late PN strategy (Mehta et al. 2016). PN may be initiated sometime during the first week, to avoid hypoglycaemia and cumulative nutrient deficiencies, especially in newborns or those with severe malnutrition at baseline. A prudent approach to advancing PN as supplement or alternative to insufficient EN in select cases, by Day 4 in the ICU, was shown to improve infection rates in adults when compared to a late PN initiation strategy (Heidegger et al. 2013). **Figure 5** summarises some of the strategies that have been employed to reduce complications and side effects in cases of chronic PN dependence. Overall, careful assessment to detect high risk patients, emphasis of early initiation and advancement of EN using algorithms, and prudent use of PN for select cases with particular attention to avoiding overfeeding, is a reasonable strategy for utilising the optimal route of nutrient delivery during acute critical illness. **Figure 6** illustrates elements of a prudent EN and PN strategy during the first week of ICU admission.

> “enteral nutrition is preferred, with early initiation in small volumes and gradual advancement as tolerated”

Summary and Future Directions

Malnutrition, including obesity, negatively impacts outcomes from critical illness. Critically ill children do not always respond to critical illness with hypermetabolism and often have decreased energy requirements. Overfeeding, from inaccurate estimates of energy requirement, must be avoided. Indirect calorimetry is a critical tool that guides energy prescription in the ICU. The ‘less is more concept’ is most applicable to energy delivery during early acute critical illness, when endogenous energy production, anabolic resistance and risk of overfeeding preclude the benefits of an early and aggressive nutrition strategy. On the other hand, protein breakdown is a principal feature of critical illness metabolism, and optimal protein delivery to offset losses may help preserve lean body mass during prolonged critical illness. Both energy and protein targets must be individually determined for each patient; a ‘one size fits all’ approach for dose, timing and route of nutrient delivery is not reasonable. EN remains the preferred route of nutrient delivery in critically ill children. Early initiation, stepwise advancement with careful assessment for safety and management of intolerance, and avoidance of unnecessary interruptions are features of a prudent EN strategy. Aggressive use of early PN is harmful and must be avoided. A pragmatic

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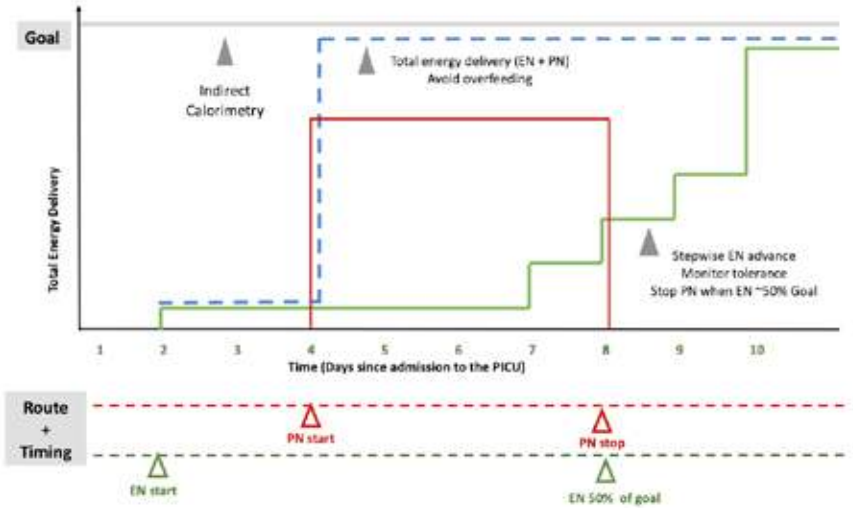

Figure 6. Stepwise EN algorithm. Source: Hamilton et al. 2014.

approach for individualised timing of PN as a supplement to insufficient EN, aiming for at least 2/3rd of the prescribed energy goal by the end of the first week of illness is recommended. Optimal PN strategies may offset its side effects and allow effective use in select patients.

Future trials will need to demonstrate the impact of nutrition strategies on long-term functional outcomes in patients. These trials will need innovative designs with high external validity and testing of the nuances of nutrition delivery. Adoption of common/uniform data elements will allow comparisons between the impact of nutritional strategies on meaningful outcomes. Muscle mass and function preservation is one of the key goals of nutrition during critical illness, and a variety of techniques to measure muscle mass and function are being investigated. There is significant interest in exploring other therapies such as early mobilisation, physical rehabilitation, exercise, and muscle stimulation to help achieve this goal (Choong et al. 2018). The role of nutrition in combination with these non-nutritive therapies must be explored (Wischmeyer et al. 2017). The future of nutrition lies in pragmatic individualised therapies that help children recover from critical illness with minimal impact on their long-term development, function and quality of life. ■

Key points

- Critically ill children do not always respond to critical illness with hypermetabolism and often have decreased energy requirements.
- Overfeeding, from inaccurate estimates of energy requirement, must be avoided - indirect calorimetry is a critical tool that must be used to guide energy prescription in the ICU.
- Enteral nutrition is preferred and is feasible in a majority of critically ill children.
- Parenteral nutrition use soon after admission to the PICU is not beneficial as a uniform strategy, and may be deferred during the first week in the PICU.
- Muscle mass and function preservation are key goals of nutrition during critical illness using optimal nutritional therapies in combination with non-nutritive strategies.

Abbreviations

ASPEN	American Society for Parenteral & Enteral Nutrition
EN	Enteral nutrition
GRV	Gastric Residual Volume
IC	Indirect calorimetry
ICU	Intensive Care Unit
OBS	Observational Study
PICU	Paediatric Intensive Care Unit
PN	Parenteral nutrition
RCT	Randomised controlled trials
SCCM	Society of Critical Care Medicine

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ESICM Satellite Symposium 2018

Chairpersons of the Satellite Symposium: *Todd Rice, Nashville, United States; Carole Ichai, Nice, France*

The Expanding Boundaries of ICU Nutrition

This symposium explores the different aspects of nutrition in the ICU and how nutritional requirements of the critically ill patient are met effectively. There is an overview of nutritional monitoring practices and how we could improve them for better nutritional delivery. There is also an overview of the DIVINE study which investigates the use of different nutritional formulas to facilitate blood glucose control in critically ill overweight and obese patients. Finally, there is a discussion on the association between skeletal muscle wasting and weakness in the critically ill patient.

What did we learn from nutritional monitoring?

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Switzerland

Monitoring nutrition in the ICU is significantly different from monitoring other activities. For example, if we look at haemodynamics, it is pretty easy. We can monitor blood pressure, cardiac output etc. We can deliver a drug and look at its effect to see if it works or not, and, if it doesn't, we can simply change the drug. These are simple activities that we do in the ICU every day.

But is the same true for nutrition? It is possible to monitor the compound we deliver, but how do we monitor the effect? How do we determine the effect of enteral nutrition, for example? How do we measure that? How do we see the side effects? Even if we observe intolerance to enteral nutrition, can we say for sure why that is so? Maybe it's because of the patient's disease itself or some other reason. The point is that if we cannot measure what we actually do, how can we know what products we should administer?

Large scale, pragmatic trials are needed to better understand this. A study, yet unpublished, was conducted with 220 patients in our 39 bed mixed surgical medical ICU. There is a nutrition protocol in place, and the assumption is that nutrition is monitored adequately. But findings from this study will clearly demonstrate that this is not the case.

Figure 1 depicts the daily administered calories per patient. As is clearly evident, there is no consistency. During the first 10 days, administered calories range from zero to 2500 or 3000 calories. Calories level off and go up 1500 calories after 10 days. This is clear evidence that nutrition is not being monitored adequately.

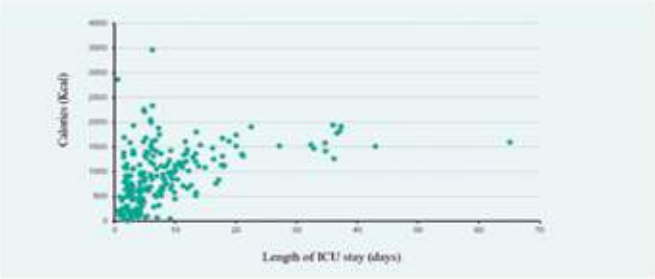

Figure 1: Daily administered nutritional calories per patient

Several reasons were considered to explain this inconsistency in daily nutritional delivery to patients, including:

- Nutritional calories vs. patient weight
- Nutritional calories vs. age
- Nutritional calories vs. daily fluid balance
- Nutritional calories vs. daily stool events
- Nutritional calories vs. number of transports out of ICU
- Nutritional calories vs. number of RASS+2 assessments/d
- Patients with catecholamine infusion

However, none of these explained the high heterogeneity of the amount of administered calories.

Figure 2 demonstrates another example of deviation between the nutrition that the patient should receive versus the nutrition that they actually receive.

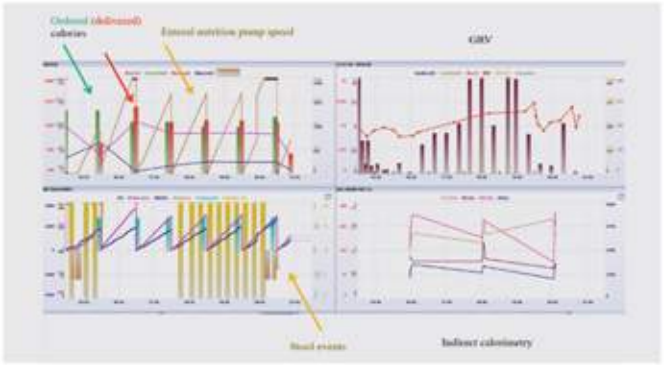

Figure 2: Nutrition delivery to the patient

The above figure clearly shows that during the first three days, this patient didn't get an order for calories for nutrition and didn't get any nutrition. In the next three days, they got some nutrition but there was no order. This was probably because the nurses started the nutrition protocol as they never received an order to do so. On day four, the doctor made the order, but the order that is delivered the next day is only half as is demonstrated by the decrease in the red column. Nothing is delivered the next day. Similarly, if we evaluate the gastric residual volume (GRV), we see that it is at 260 although our protocol says we can go up to 500 GRV. The first three days are okay as demonstrated here but then there are no orders. It is thus evident that there is no consistency in nutritional delivery. Sometimes there is an order but little delivered; sometimes, more orders are placed, and nothing is delivered; sometimes orders are placed, but half is delivered. There is no explanation for this discrepancy.

These examples indicate the need to improve how we monitor nutrition. It is important to monitor what is ordered and what is delivered, including meals. Nutrition should be monitored per kg of weight per patient and by determining how many calories the patient needs, and how much protein the patient needs. Any gaps should be documented so that clinicians know that there is a gap and they can then address it. It is also important to measure non-nutritional calories such as those obtained through citrate renal replacement therapy, dextrose infusion, or propofol[1] in order to avoid the risk of overfeeding. If nutritional calories are adapted, too little protein may be delivered. This can be an important issue in certain patients such as those who need prolonged sedation, or those with traumatic brain injury etc.

Delivery of the right amount of protein is very important. In a retrospective study by Arthur van Zanten and his group[2], they looked at patients who received less than 0.8g/kg/day and those who received more. The results showed that patients who received less than 0.8g/kg/day had the highest mortality. Patients who showed the best result were those who received less protein in the beginning, but then after three days, they received more protein, which seems like a good strategy.

Overall, it is evident that nutrition monitoring is as important as haemodynamic monitoring so as to determine any variability between recommended and delivered calories and proteins, and if such variability exists, the reasons for these differences should be documented, and concrete steps should be taken to correct the situation. Also, a large part of nutrition management in the ICU is left to the nurses, and while they do a good job, it is important that they receive support from the doctors so as to deliver adequate nutrition and follow protocols.

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ESICM Satellite Symposium 2018

Chairpersons of the Satellite Symposium: *Todd Rice, Nashville, United States; Carole Ichai, Nice, France*

DIVINE nutritional management in ICU

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The following is an overview of the DIVINE trial (Dietary Management of Glucose Variabilty iN thE ICU) as well as a quick summary of the role of glucose control and outcomes in critically ill patients. The DIVINE study was funded by Nestlé.

Clinical studies show that goal nutrition may not result in the best outcomes. Available data suggest that protein may be more important than non-protein calories. Findings from a study conducted by Peter Weijs[3] and their group show that early protein intake at a level of ≥1.2 g/kg at day 4 of ICU admission is associated with lower mortality and early energy overfeeding is associated with higher mortality in non-septic mechanically ventilated critically ill patients.

Another study[4] shows the association of administered calories/resting energy expenditure with mortality and protein intake. Findings show that the lowest mortality was observed among those who were within 60 to 80% of their goal calories whereas protein mortality was almost linear, thus suggesting that mortality goes down with more delivery of protein.

Hyperglycaemia is common in critically ill patients for a number of reasons, one of which is that critical illness worsens insulin sensitivity and resistance. It is thus associated with the severity of critical illness. This is also a probable cause of worse outcomes. It is not just the levels of glucose, but it's actually the variability of the glycaemic variability index that accounts for these outcomes. A clinical study[5] was conducted with 759 patients to evaluate glycaemic variability and its association with outcomes. Out of the 759 patients, 651 survived, and 108 died. Among the factors that could be associated with death, glycaemic variability was also highlighted, defined in this study as the standard deviation/mean blood glucose x 100. Hyperglycaemia and hypoglycaemia may both worsen outcomes.

In the NICE-SUGAR study[6] conducted with 6000 sepsis patients, and two different randomised sugar targets, it was found that in both of those groups, hypoglycaemia was associated with worse outcomes, specifically worse mortality. The more severe the hypoglycaemia, the higher the association with outcomes suggesting a dose-response. The more severe and the longer the hypoglycaemia, the bigger the hazard ratio for mortality.

The objective of the DIVINE[7] study was to determine whether blood glucose control could be facilitated by using enteral nutrition formula that contained low carbohydrates, medium-chain triglycerides and very high levels of hydrolysed whey protein to ensure optimal protein delivery. It is an open-label, multi-centre trial at seven academic medical centres in North America. The trial went on for almost two years and included mechanically ventilated, critically ill obese and overweight patients (BMI between 26 and 45) who were thought to require enteral nutrition for at least five days. Patients with hepatic failure or those admitted for trauma or major surgery or pregnant were excluded from the study.

The control group received a high protein formula, and the experimental group received a very high protein formula with low carbohydrates. The control formula had a caloric density of 1, and so did the interventional formula. But it had lower protein and higher carbohydrate with similar amount of fat as the experimental protein. The goal in both of the groups was to try and deliver 1.5 g/kg IBW/day of protein.

The endpoint of the study was the rate of glycaemic events outside of the interval of 6.1 to 8.3 mmol/L in the first seven ICU days. Secondary endpoints included serial blood glucose, markers of nutritional status, urine/serum ketones, insulin, and dextrose administered, and clinical outcomes. A total of 105 patients were randomised. 102 patients had glucose measurements that allowed them to be included in the intention to treat analysis.

Both groups received similar amounts of protein, but the experimental group received fewer carbohydrates. The experimental group got about half as much carbohydrate as the control group, and fat was similar between the two.

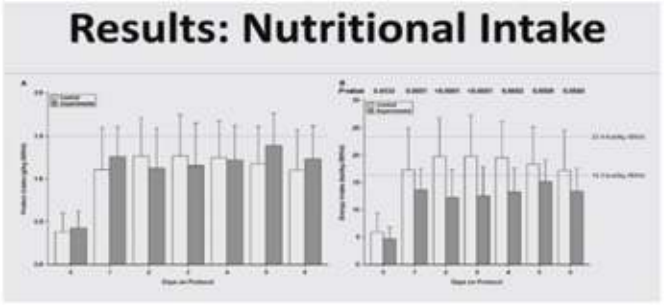

Figure 1: Results of the DIVINE study

Both groups got about 70% of their target. There was no difference in the rate of glycaemic events outside of the interval of 6.1 to 8.3 mmol/L. There was a significant increase in the mean rate of glycaemic events that were between 4.4 to 6.1 mmol/L. This was an area of concern and the primary reason why the trial was stopped. There was also a significant decrease in values above 8.3 mmol/L.

The mean glucose was significantly lower in the experimental group: 7.0 versus 7.7 mmol/L. There was no difference in the rates of hypoglycaemia defined as glucose levels less than 4.4 mmol/L. There was a smaller glycaemic dispersion in the experimental group. The experimental group also received less insulin, so there was less insulin administered both in the amounts and the number of administrations in the experimental group and no difference in the amount of rescue dextrose that was given.

There was some increased frequency of abdominal distension in the experimental group, but overall the number of patients with adverse events in both groups weren't different. Mortality, in general, was low in this trial but it was numerically lower in the intervention group than in the control group but not statistically significant. Why did patients get better control in the experimental group? There could be a number of potential reasons for this, and multiple of these could be at play.

One is that a higher protein load probably improves insulin sensitivity. The second is the type of protein matters, and whey protein improves insulin sensitivity. The third is that if you give fewer carbohydrates, you probably have better glucose control. In general, if you give fewer calories, you actually have better glucose control.

To summarise the findings of the DIVINE study, a very high hydrolysed whey protein low carbohydrate formula facilitated blood glucose control in critically overweight and obese patients. Although it didn't reduce the number of events outside of the interval of 6.1 to 8.3 mmol/L, it did lower dispersion of blood glucose as measured by standard deviations and had a lower incidence of hyperglycaemia defined as glucose > 8.3 mmol/L.

Nutritional support for critically ill patients needs to be individualised, and that includes individualised plans for obese patients. Current data suggest that moderate permissive underfeeding while administering higher levels of protein may improve outcomes of critically ill obese patients. Avoiding hyper and hypoglycaemia likely does improve outcomes, and as this study suggests, that can be accomplished by specific nutritional formulas. Further research is required to see if these nutritional formulas actually improve clinical outcomes and not just blood sugar control.

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ESICM Satellite Symposium 2018

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The metabolic phenotype of skeletal muscle during early critical illness

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The Muscle UK Critical Care program was set up 10 years ago and focused on the association between muscle and skeletal muscle wasting to weakness to clinical outcome. There are a total of five pivotal trials, including Bernhard Jonghe et al.[8] and Herridge M.[9] that looked at skeletal muscle weakness and its impact on patients. In the Herridge study, all patients reported poor function and attributed this to loss of muscle bulk, proximal weakness, and fatigue.

According to the National Institute of Clinical Excellence, the lack of detailed understanding of the pathophysiology of muscle wasting must be addressed. Data from early mobilisation trials do not show enhanced functional capacity and improved health-related quality of life in critical illness survivors.

There is a huge array of studies which have shown the impact of critical illness on skeletal muscle - both the diaphragm and peripheral skeletal muscle. It occurs rapidly and early. It can be exceptionally pronounced. Diaphragm dysfunction is twice as frequent as peripheral muscle weakness and diaphragm and limb weakness are predictors of clinical outcome. The severity of the illness determines the degree of muscle wasting and the chronic health that the patient actually enters the ICU determines their trajectory of recovery.

A comprehensive study[10] was conducted to characterise skeletal muscle wasting and to define the pathogenic roles of altered protein synthesis and breakdown. It was observed in these studies that muscle wasting was significantly greater in the sickest patients.

Critically ill patients are wasting away. If we look at studies done with biopsies at day 1 and day 7, the critical care patient is the same in terms of muscle protein synthesis. However, muscle protein breakdown is high and remains high throughout that first week of critical illness.

A study was conducted by Puthucheary et al.[11] which investigated if adenosine triphosphate (ATP) bioavailability and lipid metabolism are drivers of early and rapidly acute skeletal muscle wasting that occurs during critical illness. As demonstrated in the study, the ATP in the control group reduced from day one to day 7. In other words, energy declined. There was also a decline in phosphocreatine from day one to day 7. Creatine remained the same from day one to day 7.

Glucose is also a central component. Fat is utilised through beta-oxidation, and it's really key. If we don't utilise glucose, we would need another energy substrate. In critically ill patients, what we see over the first week is a reduction in mitochondrial biogenesis as patients do not produce the same number of mitochondria. This results in a reduction in mitochondrial DNA copy number as well as a reduction in mitochondrial beta-oxidation enzyme numbers. Mitochondrial beta-oxidation falls in the first week, and there's a reduction in lipid metabolism, and not surprisingly there's a rise in intramuscular phosphate lipids. Therefore, we're increasing the amount of lipid that's actually in the muscle.

Decreased ATP, decreased creatine, and decreased phosphocreatine availability are directly and closely related to acute skeletal muscle wasting. The activation of the hypoxic inflammatory signals is closely related and directly related to the impairment of the anabolic signaling pathway/ Injured muscular ATP is skeletal muscle matter unrelated to the quantity of lipids that are being delivered. There is a relationship between loss in muscle mass in early critical illness and skeletal muscle bioenergetic status, inflammatory, hypoxic and protein homeostatic signalling ***(Figure 1)***. Skeletal muscle wasting in critical care is associated with impaired lipid oxidation and reduced ATP bioavailability, driven by intramuscular inflammation and altered hypoxic signalling, which may account for the inconsistent outcome observed in the nutrition and exercise clinical trials.

Figure 1. Skeletal Muscle Wasting

Key take-home messages from this discussion are as follows:

- Decreased ATP, creatine, and phosphocreatine availability are closely and directly related to acute skeletal muscle wasting.
- Activation of hypoxic and inflammatory signaling are closely and directly related to impairment of anabolic signaling pathways.
- Changes in intramuscular ATP content and skeletal muscle mass are unrelated to the quantity of lipids delivered.

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Nestlé Health Science
Clinician Lunch Symposium

ESICM LIVES 2019

Appropriate nutrition is integral to patient care

Monday 30th September 2019
12:30 - 14:00 | Room Paris
Chair: Prof. Mette M. Berger

Topics & Presenters

- **Smart nutrition not more nutrition.**
  Dr. Zudin Puthucheary, UK
- **Can nutrition be used to target mitochondrial dysfunction?**
  Prof. Mervyn Singer, UK
- **Update 2018 ESPEN guidelines.**
  Prof. Mette M. Berger, Switzerland
- **Increased protein delivery while decreasing carbohydrate loads.**
  Dr. Juan B. Ochoa Gautier, USA

Nestlé Health Science
Nurses and Allied Health Professional Lunch Symposium

The nurse is the cornerstone of *nutrition delivery*

Tuesday 1st October 2019
12:30 - 13:30 | Room Arena

Topics & Presenters

- **Nurse driven metabolic care.**
  Prof. Mette M. Berger, Switzerland
- **A nursing perspective on nutrition.**
  Béatrice Jenni-Moser, ICU Clinical Nurse Specialist, Switzerland

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Obesity and Nutrition in Critical Illness

The role of nutrition in obese critically ill patients and an overview of the clinical guidelines for nutrition provision in this patient population.

Introduction

The World Health Organization defines obesity as an excess of abdominal fat that poses an increased risk to health. Characterised by a body mass index (BMI) ≥30 kg/m^2, obesity rates have tripled since 1975, and in 2016, 650 million people worldwide were obese (who.int/news-room/fact-sheets/detail/obesity-and-overweight). In the largest analysis of international nutrition provision during critical illness (n=17,154), more than half of the patients were overweight or obese, and the mean and standard deviation (SD) BMI was 27 (8) kg/m^2 (Ridley et al. 2018). Moreover, in the most recently published and largest critical care enteral nutrition trial ever conducted, the impact of higher energy enteral feeding versus standard care nutrition on 90-day survival was investigated (3957 patients from 46 ICUs in Australia and New Zealand). The mean (SD) BMI in the intervention and standard care groups was 29.2 (7.7) kg/m^2 and 29.3 (7.9) kg/m^2 respectively (Chapman et al. 2018). Obesity is associated with increased morbidity in the general population, but the impact of obesity in critical illness on clinical outcomes is more complex. While obesity is associated with increased morbidity and resource utilisation, a J-shaped relationship exists where overweight and moderate obesity is protective of mortality compared to a normal BMI or severe obesity [known as the obesity paradox] (Arroyo-Johnson and Mincey 2016; Schetz et al. 2019).

Clinical Guidelines Informing Nutrition Provision in Obese Critically Ill Adults

Published first, The American Society of Parenteral and Enteral Nutrition (ASPEN) Clinical Guidelines: Nutrition Support of Hospitalized Adult Patients inform the ASPEN/Society of Critical Care Medicine Guidelines for the Provision and Assessment of Nutrition Support Therapy. Both of these guidelines recommend hypocaloric energy provision (lower than measured or estimated energy expenditure) with high protein intake for hospitalised and critically ill obese patients based on 2 available RCTs and limited observational evidence (Choban et al. 2013; McClave et al. 2016). Hypocaloric energy provision is recommended as obese hospitalised patients are at increased risk of metabolic complications if overfeeding occurs (Choban et al. 2013). The basis for the higher protein recommendations is to modulate catabolism and facilitate protein anabolism. The amount of protein recommended increases with class of obesity and are based on data from 163 patients in total (**Table 1**) (Choban et al. 2013; McClave et al. 2016). It must be noted that the recommendations are being extrapolated to critically ill obese patients when only some of the data have been derived in this population, and positive nitrogen balance and protein anabolism is very difficult to achieve in critical illness due to catabolic metabolic processes, especially in the early phase of illness. However, it is entirely plausible that protein may be more important than energy in critical illness, and this may vary depending on phase of illness; however, as with the general critically ill population, definitive data is required to understand this. In contrast, the most recent European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines on clinical nutrition in the ICU recommend isocaloric energy intake with 1.3 g/kg of protein using an

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Table 1. Clinical nutrition guideline recommendations for critically obese patients

Guideline	ESPEN	ASPEN
Commencement of nutrition support	No specific statement	Within 24 hours where normal intake is not possible/inadequate (EC)
Energy	• Iso-caloric high protein diet (Grade 0) • Indirect calorimetry preferred over predictive equation (Grade 0) General recommendation for all ICU patients • In the early acute phase of illness aim for <70% (before day 3) (Grade B) • After day 3, increase to 80-100% of measured or estimated REE	• Indirect calorimetry preferred over predictive equation (EC) • If IC used, target 65-70% of a measured requirement (for all classes of obesity) (EC) • If IC unavailable (EC); BMI 30-50 kg/m^2; 11-14 kcal/kg ABW BMI >50; 22-25 kcal/kg/IBW
Protein	• Guided by urinary nitrogen loss or lean body mass determination (GPP) • If the above not possible, 1.3g / kg ABW (GPP)	• BMI 30-40; 2 kg IBW/day (EC) • BMI ≥ 40; 2.5 g/kg IBW/day (EC)
Weight adjustment	3 methods proposed for BMI >25 (not graded): • IBW: 0.9 x eight in cm- 100 (male) (or 106 (female)) • For energy requirement calculation; Add 20-25% of the excess body weight (actual body weight-ideal body weight) to the IBW as above • For protein; 'adjusted body weight'; IBW+ 1/3 actual body weight	• No specific statement

ABW: actual body weight; BMI: Body mass index; BW: body weight; EC: Expert consensus; GPP: Good practice point; IBW: Ideal body weight; REE: Resting energy expenditure

adjusted body weight (Singer et al. 2018). **Table 1** summarises the ASPEN (McClave et al. 2016) and ESPEN (Singer et al. 2018) clinical guideline recommendations for the nutrition management of critically ill obese patients.

Evidence Informing Nutrition Provision in Critically Ill Obese Adults

Minimal high-quality research exists investigating the impact of nutrition on clinical and functional outcomes in critically ill obese patients. Two, double-blind, randomised controlled trials (RCTs) have been conducted over 20 years ago. Including less than 50 patients in total, both investigated hypocaloric, high protein PN interventions, only one was conducted in a critically ill population, and both were clearly underpowered to investigate important clinical outcomes (Burge et al. 1994; Choban et al. 1997). **Table 2** provides a summary of these trials. Conversely, the largest observational analysis available (162 critically ill patients with a BMI of 35-40 kg/m^2 out of a total sample of 2772) found a significant survival association with additional energy and protein above standard care (Alberda et al. 2009). This finding can only be considered hypothesis generating despite statistical adjustment and analysis due to the considerable risk of confounding. Furthermore the previously mentioned enteral feeding trial (The Augmented Versus Routine Approach to Giving Energy Trial), enrolled the largest cohort of critically ill obese patients within a robust RCT design (n=1423 with a BMI ≥ 30 kg/m^2). The treatment effect on 90-day survival was not statistically significant although the obese sub-group was the only group where the point-estimate favoured the intervention of higher energy delivery (Chapman et al. 2018). Importantly, patients in both groups received the same amount of protein (1.1g/kg ideal body weight/day).

> "methods to objectively measure or predict whole-body muscle in critically ill patients are limited"

Considerations for Clinicians

For clinicians to fully understand the impact of nutrition in obese critically ill patients, several fundamental issues need to considered and robustly investigated. Firstly, commonly used predictive equations are less accurate in overweight and obese patients compared to those of normal weight. This is probably due to the most commonly used equations being developed in non-obese populations but applied in those with obesity, coupled with the considerable variation in body composition in individuals who are obese (Frankfield et al. 2005; Frankfield et al. 2013). For example, an obese person can carry a high muscle mass, be very physically active, and be metabolically healthy, or they can suffer from malnutrition and sarcopenic obesity. This variation in body composition is also why the use of BMI as a 'marker' of obesity is sub-optimal as it does not consider the distribution of muscle and adipose tissue (Choban et al. 2013). However, the assessment of muscularity is

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challenging in the ICU setting, and obesity adds another element of difficulty with excessive adipose tissue making a physical assessment almost impossible (Sheean et al. 2014). Currently, methods to objectively measure or predict whole-body muscle in critically ill patients are limited (Earthman 2015). CT image analysis at the third lumbar area can be used, although this technology needs specialist training and is clearly limited to a select group of patients who have a CT scan at L3 (Paris and Mourtzakis 2016; Price and Earthman 2019).

Ultrasonography and bioimpedance analysis show promise and studies are underway to investigate these methods further, although use in the obese population may be limited (clinicaltrials.gov/show/NCT03019913). Variations in body composition can also cause significant differences in metabolic rate (high in those with increased muscle mass and low in those with sarcopenia) and the response to nutrition delivery may hence be varied. Clinicians should, therefore, consider that metabolic rate is likely to be variable in obese critically ill patients. In a recent cohort study of 25 critically ill patients with a BMI ≥ 30 kg/m^2, the mean measured resting metabolic rate (RMR) using indirect calorimetry was 2506 (749) kcal. The predicted energy requirement using the ASPEN guidelines recommendation of 11-14 kcal/kg/actual body weight was 1080 (200) and 1375 (254) kcal/day, respectively (Vest et al. 2019). This is an alarming difference when there are no definitive data on the clinical and functional consequences of hypocaloric feeding strategies in obese critically ill patients. In contrast, a recent RCT investigating the use of indirect calorimetry (intervention) to guide nutrition delivery compared to a predictive estimate (standard care) included patients with a median BMI of approximately 22 kg/m^2. In this population who were largely in the healthy weight range, the median RMR (interquartile range) was 2069 (1816–2380) kcal in the intervention group and 1887 (1674–2244) kcal in the standard care (Allingstrup et al. 2017). It is therefore plausible that in some obese patients, energy expenditure may be higher than predicted by equations (especially in the acute flow phase of illness). Given the differences observed between measured estimates and the ASPEN hypocaloric nutrition guidelines, it is hypothesised that a minimum weight loss of 2-3 kg per week could be induced if nutrition were prescribed according to these guidelines (Singer et al. 2018). Furthermore, clinicians should be aware that when aiming for full target nutrition during critical illness, patients almost always receive approximately 50-60% of this goal for multifactorial reasons (Ridley et al. 2018; Passier et al. 2013). It is likely that if hypocaloric nutrition is purposefully aimed for, even less will be achieved, without understanding the clinical and functional impact. Finally, a large observational analysis of 3257 ICU stays investigated the association of BMI with the timing of the commencement of nutrition support. A BMI ≥30 kg/m^2 (n=663/3257) was independently associated with a longer time to initiation of nutrition than any other BMI category (relative risk for delayed nutrition commencement in obese patients; 1.06 (1.00, 1.12) for obese patients, P = 0.004) (Borel et al. 2014). The reason for this was not examined, but it could be hypothesised that it reflects an assumption that commencement of nutrition in obese critically ill patients is not prioritised as it is in those of normal or low body weight.

> **“a minimum weight loss of 2-3 kg per week could be induced if nutrition were prescribed according to the ASPEN guidelines”**

Clinical Implications for Clinicians

It is the opinion of the authors that until definitive research is achieved as to the impact of energy and protein delivery on clinical and quality of life outcomes, critically ill obese adults, be managed as any other critically ill patient. Evidence from a number of large RCTs suggests that the amount of energy delivered during the first week of ICU has no impact on survival or functional outcomes (Needham et al. 2013). Given the inaccuracy of predictive equations, indirect calorimetry is preferred to calculate energy expenditure. If predictive equations are used, an adjusted weight should be calculated to account for excess adiposity for both the energy and protein estimations. Consideration to body composition and premorbid function should also be given and may inform expected energy expenditure (high or low). Enteral administration of some nutrition should be commenced as early as possible during the ICU stay and increased to goal as tolerated. Inability to deliver full energy goals in the first week of the ICU stay should not result in the initiation of extraordinary treatments (such as the administration of prokinetics, the placement of small intestinal feeding tubes or the intravenous administration of nutrition) as these treatments may have adverse effects and no benefit on outcome has been demonstrated early in ICU stay. After the first week of ICU stay, 80-100% of energy and protein goals should be achieved based on the possibility that significant weight loss during a catabolic period may lead to the development of sarcopenia with persistent obesity, compromising functional recovery. As recommended in ESPEN guidelines, a protein intake of at least 1.3 g/kg adjusted body weight *delivered* should be the aim until definitive evidence is achieved as to the impact of higher protein delivery on clinical and functional outcomes (Singer et al. 2018). Moreover, achieving higher protein delivery is difficult with current commercially available products, and without definitive evidence seems unnecessary. It

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Table 2. Randomised trials informing recommendations for nutrition in obese critically ill patients

Paper	Trial details			Intervention			Control			Outcomes
	Population	n	Study aim and details	Energy	Protein	Actual intake Mean (SD)	Energy	Protein	Actual intake Mean (SD)	
Choban et al, 1997	Obese adult patient referred for PN (13 patients in ICU)	30	To assess the efficacy of hypocaloric vs eucaloric PN with protein at 2 g/kg IBW Double blind	Hypocaloric Aim for kcal/nitrogen ratio of 75:1	High protein	1293 (299) kcal and 120 (27)g protein	Eucaloric Aim 150:1 kcal/nitrogen ratio	High protein	1936 (198) kcal and 108 (14) g protein (1.2 g/kg actual weight, 2 g/kg IBW)	Weight change; 0 (6.3) kg (Hypocaloric) vs 2.7 (7) kg (Eucaloric)
Burge et al, 1994	Hospitalised obese patients referred to nutrition service for PN	16	To determine if nitrogen balance could be maintained in patients receiving hypocaloric, high protein PN Double blind	Hypocaloric 50% REE; kcal/nitrogen ratio of 75:1	High protein	1285 (374) kcal (14 kcal/ABW) and 111 (32) g protein (1.3 g/kg ABW, 2 g/kg IBW)	Eucaloric 100% of REE; aim 150:1 kcal/nitrogen ratio	High protein	2492 (298) kcal (25 kcal/kg/actual weight) and 130 (15) g protein (1.2 g/kg or 2 g/kg IBW)	No clinical outcomes reported Weight change; - 4.1 (6)) kg (Hypocaloric) vs – 7.4 (8.4) kg ((Eucaloric)

ICU: Intensive Care Unit; IBW: Ideal body weight PN: parenteral nutrition; SD: standard deviation

Key points

- Obesity is associated with increased morbidity in the general population, but the impact of obesity in critical illness on clinical outcomes is more complex.
- Clinical guidelines recommend hypocaloric energy provision with high protein intake for hospitalised and critically ill obese patients.
- Commonly used predictive equations are less accurate in overweight and obese patients compared to those of normal weight, and indirect calorimetry is preferred to calculate energy expenditure.
- Clinicians should manage the nutrition of the obese critically ill patient as any other patient; conservatively in the first week of ICU stay, with an aim to meet energy and protein requirements after this time.

may be appropriate to consider a weight loss regime once transitioned to the ward; however, this should be assessed on an individual basis with a multidisciplinary team.

Conclusion

The need for a robustly designed and systematic programme of research to investigate the role of nutrition in obese critically ill patients has been recommended since 2002 and most recently in an important clinical guideline; however no RCTs have been performed, and there are none registered on any major trial registries (Choban et al. 2013; Dickerson et al. 2002). Well-designed and adequately powered studies are now urgently needed to understand the energy and protein requirement to target, the impact of energy and protein delivery, and to address the important question of whether a hypocaloric, high protein diet improves important clinical and functional outcomes in obese critically ill adults. Until such time it is recommended that clinicians manage the nutrition of the obese critically ill patient as any other patient; conservatively in the first week of ICU stay, with an aim to meet energy and protein requirements after this time, recognising that metabolic rate may be highly variable based on body composition, and prolonged starvation may impact functional recovery. ■

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Objective Malnutrition Diagnosis and Personalised Nutrition Delivery in the ICU

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Poor ICU nutrition delivery remains a challenge worldwide. Objective malnutrition diagnosis and personalisation of nutrition delivery may be one way of addressing this problem.

Modern, and increasingly expensive ICU care now allows prolonged survival from illness and injury by providing life-sustaining support for extended periods of time, making previously nonsurvivable ICU insults, survivable. In fact, innovations in ICU care have resulted in yearly reductions in hospital mortality from sepsis (Kaukonen et al. 2014). However, these same data reveal many ICU "survivors" are not returning home to functional lives post-ICU; but instead to rehabilitation settings where it is unclear if they ever return to a meaningful quality of life (QoL) (Kress and Hall 2014). ICU acquired weakness (ICU-AW) is a common complication of critical illness. A hallmark of ICU-AW is reduced muscle mass and strength, which both are independent predictors of ICU survival (Weijs et al. 2014).

Muscle mass and quality derived by CT scans in mechanically ventilated patients, is associated with a 6-month higher mortality (Weijs et al. 2014; Looijaard et al. 2016; Looijaard et al. 2018). Tragically, an increasing number of patients who survive ICU suffer from severe, prolonged functional disabilities (Kress and Hall 2014; Hopkins et al. 2017; McNelly et al. 2016; da Silveira et al. 2018). Recent data shows ICU patients (mean age: 55) are likely to be discharged to post-acute care facilities and incur substantial costs of ~$3.5 million/functioning survivor (Herridge et al. 2016). Unfortunately, post-ICU functional disability is most common and most severe in survivors requiring time on a ventilator for respiratory failure, where recent data shows 2 out of 3 ICU survivors (65%) suffer significant functional limitations (Kress and Hall 2014). *Thus, it must be asked in modern ICU care, "are we creating survivors…or victims?"* This is a defining challenge for modern critical care all major ICU societies have recommended giving priority to research addressing post-ICU QoL outcomes in these survivors (Needham et al. 2017).

To improve functional and QoL outcomes in acute renal failure (ARF) survivors, one obvious low-cost therapeutic strategy that can be rapidly implemented is objective, data guided personalised nutrition delivery to attempt to maintain and allow recovery of muscle mass/function. This is particularly essential in patients with pre-existing and subsequent iatrogenic malnutrition that commonly occurs in ICU patients. In fact, despite increasing obesity rates in many countries, preexisting malnutrition is highly prevalent in ICU patients- with as many as 1 in 2 (30-50%) patients being malnourished at ICU admission(Normal et al. 2008). Unfortunately, unrecognised malnutrition in the hospital and ICU may be among the most pressing "silent epidemics" facing hospitalised patients in the world today. Although it is well known that greater then 1 in every 3 hospitalised patients is malnourished at hospital admission (Barker et al. 2011), limited older data estimates only 3% of malnourished U.S. hospitalised patients are being recognised and diagnosed (Corkins et al. 2014). Thus, only 1 in 10 malnourished patients are ever diagnosed and even fewer are treated. This silent epidemic of "the skeleton in the hospital closet" has been described for >40 years (Butterworth 2005), but this data shows it has yet to be addressed. This is tragic as mortality is 5 times greater (11.7% versus 2.4%) overall for hospitalised patients diagnosed with malnutrition versus well-nourished (Corkins et al. 2014). Further, the outcomes of ICU patients with pre-existing malnutrition and sarcopenia are further complicated by the fact that critical illness is characterised by an acute catabolic response leading to rapid loss of lean body mass (LBM) contributing to muscle wasting, weakness, and loss of function (Dinglas et al. 2017; Wischmeyer 2016; Wischmeyer 2018).

Poor ICU nutrition delivery remains a challenge worldwide. *Review of current practice demonstrates the actual amount*

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Table 1. New Personalised Nutrition Care Monitoring Devices for Muscle/Body Composition and Energy Needs

Measure	Endpoint	Descrirption
Muscle Ultrasound	Muscle Mass	Ultrasound-based measurement of skeletal muscle mass as well as quality measures of intramuscular glycogen content (IMGC), intramuscular Adipose Tissue (IMAT), and muscle size (MS).
Lean Body Mass via CT Scan	Muscle Mass	Lean body mass obtained from admission abdominal CT scan. Hounsfield Unit boundaries analysed by SliceOmatic software to reflect whole-body muscle
Segmantal Bioelectrical Impedance Spectroscopy (S-BIS)	Muscle Quality/ Intracellular Water	Segmental BIS can distinguish intracellular water (ICW) and extracellular water (ECW). ICW reflects muscle cell mass, whereas ECW represents the sum of interstitial and ECW are only affected by segmental volume, so the ECW/ICW ratio could indicate the ratio of non-contractile tissue to contractile tissue regardless of assessed somatotype (age, gender, disease state).
Indirect calorimetry	Resting Metabolic Rate	Measures the oxygen consumption (V02) and the carbon dioxide (VCO2) production at the mouth (mask or ventilated hood) in a non-invasive way. V02 and VC02 corresponds to the whole-body cellular respiration and makes it possible to calculate the whole-body energy expenditure (EE) and resting metabolic rate (RMR).

of nutrition delivered primarily via enteral nutrition (EN) in ICU patients is <50% of the prescribed goal even in our most malnourished patients (Cahill et al. 2010). In an era of heightened concern about patient safety and medical error, we and others have consistently documented that critically ill patients receive, on average only 40-50% of their prescribed goal nutritional requirements for prolonged periods (>1 week) after ICU admission (Barr et al. 2004; Binnekade et al. 2005; De Jonghe et al. 2001; Heyland et al. 2003; Krishnan et al. 2003; Rubinson et al. 2004). This is particularly concerning as the average protein delivery (thought essential for muscle/functional recovery) for the first 12 days of an ICU stay is only 0.6 g/kg/d (Cahill et al. 2010), which is one-third of the guideline recommendations of 1.5-2.0 g/kg/d in ICU (Taylor et al. 2016). *This is an urgent patient safety crisis that must be addressed.* One of the major drivers of lack of emphasis on improved nutrition delivery in ICU and post-ICU patients is lack of objective data to guide "personalised ICU nutrition." Specifically, lack of objective tools to: 1) Diagnose nutrition risk objectively, 2) Determine accurate bedside energy requirement data which is known to change throughout the course of illness, and 3) Lack of quantitative assessment tools to evaluate effect of nutrition on patient. As ICU physicians would not deliver vasopressors without a continuous blood pressure measure; we believe the ICU community has not embraced a focus on nutrition delivery due to lack of objective data to guide personalised nutrition care.

> "preexisting malnutrition is highly prevalent in ICU patients with as many as 1 in 2 patients being malnourished at ICU admission"

Role of Muscle Mass, Body Composition, and Indirect Calorimetry Analysis in Malnutrition Diagnosis and Nutrition Delivery

The use of a quick non-invasive technique to evaluate skeletal muscle quantity and quality in ICU patients could have profound prognostic implications for how malnutrition is diagnosed. As stated in new Global Leadership Initiative on Malnutrition (GLIM) Guidelines (Cederholm et al. 2019), muscle mass is a new and innovative marker of malnutrition. A number of techniques are now available to assess muscle mass, lean body mass (LBM), or Fat-Free Mass (FFM) in ICU patients at bedside. Further, new and easy-to-use bedside indirect calorimetry devices have also recently been developed. Key new available techniques for ICU nutrition and metabolic analysis for the delivery of personalised nutrition are summarised in **Table 1**.

Muscle Ultrasound

Recently, we have assisted with development of a muscle-specific U/S-based technique to enable non-invasive measurement of skeletal muscle mass as well as quality measures of intramuscular glycogen content (IMGC), intramuscular Adipose Tissue (IMAT), and muscle size (MS) (Wischmeyer et al. 2017; Wischmeyer and San Millan 2015). Validation of muscle mass from U/S with gold standard techniques (such as MRI/CT scan) has been previously published (Arbeille et al. 2009). Specific to ICU, a very recent trial showed good inter-/intra-rater reliability for muscle mass U/S in acutely ill patients (Pardo et al. 2018). Further, recent data has shown increased U/S-muscle mass is correlated to improved functional handgrip strength following an a targeted ICU nutrition intervention (Ferrie et al. 2016). Thus, muscle U/S measures correlates with improved patient function and this is modifiable by improved nutrition delivery. The decline in muscle function both during and after critical illness is the result of not only a change/reduction of skeletal muscle mass but also as a result of changes in muscle quality such as muscle composition, histology and morphology (Looijaard et al. 2016; Correa-de-Araujo

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Tailoring mechanical ventilation using Ultrasound and other advanced monitoring tools
Prof. Francesco Mojoli *(Pavia, Italy)*

Opportunities where AI could support individualized ventilation strategies
Dr. Marius Terblanche *(London, UK)*

Protecting ward patients: the case for continuous monitoring
Dr. Frederic Michard *(Lausanne, Switzerland)*

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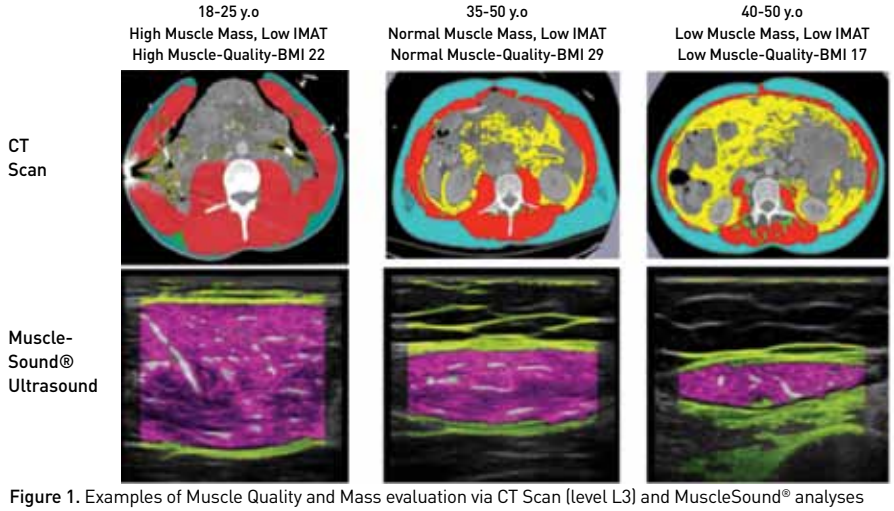
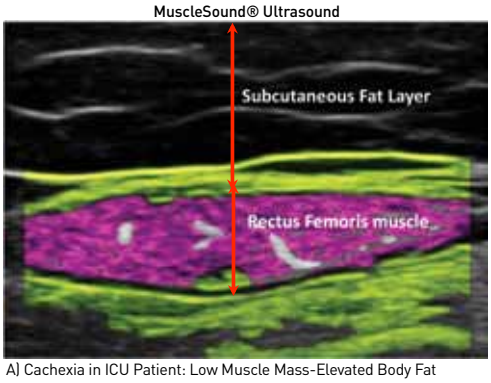
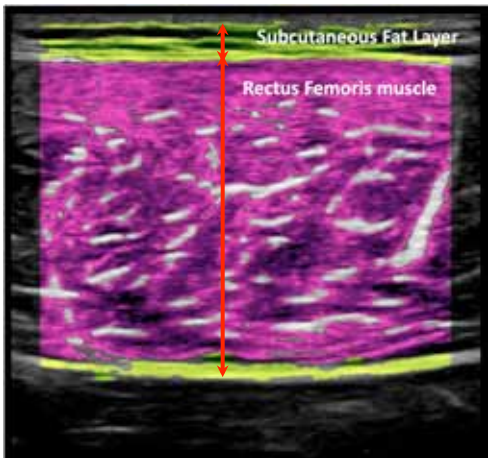


Figure 1. Examples of Muscle Quality and Mass evaluation via CT Scan (level L3) and MuscleSound® analyses (short-axis rectus femoris muscle) assessed at the same time.



A) Cachexia in ICU Patient: Low Muscle Mass-Elevated Body Fat

Bioimpedance Spectroscopy Body Composition Analysis	
Intracellular Water	12.8L
Extracelluler Water	8.8L
Dry Lean Mass	7.8kg
Lean Body Mass	29.4kg
Body Fat Mass	20.0kg
Muscle-Fat Analysis	
Weight	49.4kg
Skeletal Muscle Mass	14.7kg
Body Fat Mass	20.0kg
Obesity Analysis	
BMI	17.6kg/m²
PBF	40.5%



B): Professional Athlete: High Muscle Mass-Low Body Fat

Body Composition Analysis	
Intracellular Water	47.1L
Extracelluler Water	31.9L
Dry Lean Mass	27.6kg
Lean Body Mass	106.6kg
Body Fat Mass	10.4kg
Muscle-Fat Analysis	
Weight	117.0kg
Skeletal Muscle Mass	59.5kg
Body Fat Mass	10.4kg
Obesity Analysis	
BMI	29.3kg/m²
PBF	8.9%

Figure 2: Examples of Muscle Ultrasound of the rectus femoris muscle- and Total Body Composition analyses using MuscleSound® ultrasound analysis (muscle quality and size) and Segmental Bioelectrical Impedance Spectroscopy (S-BIS) measurements (InBody S10).

et al. 2017; Fragala et al. 2015). Skeletal muscle quality is already recognised as a marker of function in healthy individuals (Watanabe et al. 2013) and critically ill patients (Wischmeyer et al. 2017; Parry et al. 2015; Puthucheary et al. 2013; Bear et al. 2017) and has been emerging as a means to describe the changes associated with altered muscle functioning (Fragala et al. 2015; Watanabe et al. 2013; Sieber 2017; Kelley and Kelley 2017). Assessing muscle mass and quality in clinical populations at the bedside is of key importance due to the emerging associations between low muscle quality with low muscle mass and poor functional status (da Silveira et al. 2018). This allows for an increased understanding of the relationship between skeletal muscle quantity and quality, and malnutrition/outcome risk (McNelly et al. 2016; da Silveira et al. 2018). Our group has initial validation data for muscle quality from U/S versus gold-standard CT scan muscle quality and have an R2 value of 0.989 (unpublished data). Finally, Puthucheary et al reported an increase in IMAT observed in muscle biopsies during ICU stay (Puthucheary et al. 2018). They described the existence of a compromised muscle bioenergetic status as a result of a dysregulated lipid oxidation (Puthucheary et al. 2013; Puthucheary et al. 2018).

The ease of adoption of muscle U/S at the ICU bedside has been markedly improved by the availability of a muscle specific U/S device (Musclesound Inc, Colorado, USA) This handheld U/S device is easy to carry and can be connected to a portable tablet device. The device is focused on allowing rapid, accurate measures of LBM at the bedside, with built-in guidance to ensure reproducible measurements. This new device is a significant improvement in LBM U/S technology. Unique measures of muscle glycogen and muscle quality can now be ascertained at the bedside in study subjects using the Musclesound U/S. As described. muscle quality has recently been correlated to muscle strength (Akazawa et al. 2018). Muscle glycogen U/S measures have been validated via muscle biopsy (Hill and Millan 2014) and we have shown ICU patients have significant muscle glycogen deficits (Wischmeyer et al. 2017; Wischmeyer and San Millan 2015). Muscle glycogen is known to change daily based on adequacy of nutrition intake, muscle uptake of substrate and "physical stress." Thus, it could prove useful in monitoring of nutrition delivery and

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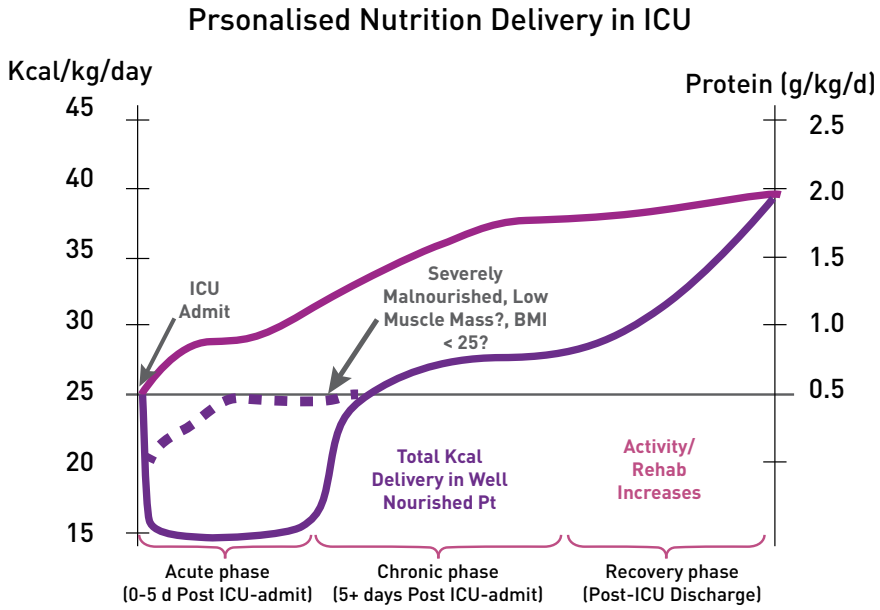

Figure 3. Hypothesised Personalised Nutritional Needs Over Time in ICU (adapted from Wischmeyer 2018)

utilisation in ICU patients. See **Figure 1** for example comparisons of muscle measures via MuscleSound and CT Scan.

Segmental Bioelectrical Impedance Spectroscopy (SBIS)

Segmental bioelectrical impedance spectroscopy (SBIS) is another non-invasive approach of muscle quality assessment via bioelectrical impedance (BIA). SBIS or BIA equipment does not measure muscle mass directly, but instead derives an estimate of muscle mass based on whole-body electrical conductivity (Cruz-Jentoft et al. 2019; Kaido et al. 2012). Skeletal muscle has a large amount of water, and SBIS can separately assess intracellular water (ICW) and extracellular water (ECW), which are divided by the muscle cell membrane. SBIS can distinguish ICW and ECW from the total water in a particular segment. Segmental BIS is advantageous for assessments of a localised (left/right) region (arm, leg and trunk) instead of only the whole-body ICW reflects muscle cell mass, whereas ECW represents the sum of interstitial fluid and blood plasma in extracellular space. The calculations of ICW and ECW are only affected by segmental volume, so the ECW/ICW ratio could indicate the ratio of non-contractile tissue to contractile tissue regardless of assessed somatotype (age, gender, disease state). The phase angle and an estimation of energy expenditure are also reported in the SBIS measurement in modern devices.

> **"unrecognised malnutrition in the hospital and ICU may be among the most pressing silent epidemics facing hospitalised patients in the world today"**

One limitation of SBIS and BIA measurements has been the concern for the effect of hydration status on measurements in the ICU (Looijaard et al. 2018). Recent research in critical illness has focused on the prognostic values of SBIS measurements such as the phase angle which are directly measured, and are not as sensitive to changes in hydration status. A multinational trial in a diverse population of 931 critically ill patients demonstrated a low phase angle at admission (day 1) was associated with increased 28-day mortality (Thibault et al. 2016). This was further validated in a recent study of 196 heterogenous ICU patients. This study showed a low phase angle at ICU admission was associated with increased 90-day mortality (Stapel et al. 2018). See **Figure 2** for example comparisons of body composition measures via SBIS (Inbody S10, Inbody Inc, California, USA) and muscle-specific U/S (Musclesound). The newly published GLIM criteria describes specific (Cederholm et al. 2019) Appendicular Skeletal Muscle Index (ASMI, kg/m2) and Fat Free Mass thresholds that may be obtained from BIA (or SBIS) for low muscle mass to objectively diagnose malnutrition.

A New Era of Indirect Calorimetry Devices for Measurement of Personalised Energy Expenditure

As shown in **Figure 3**, our research group has hypothesised that energy needs change throughout the course of illness and recovery (Wischmeyer 2018). However, this has not been validated with actual longitudinal resting energy expenditure (REE) measures, as is now possible with new metabolic cart devices (such as the Q-NRG, COSMED, Rome, Italy). As described, energy expenditure (EE) in ICU patients has been hypothesised to be highly variable based on a range of features including initial injury/illness, severity of illness (i.e. sepsis can dramatically decrease EE), nutritional status and other treatments (Wischmeyer 2018). It is also clear that clinicians ideally need to measure EE by indirect calorimetry (IC) to optimise nutritional support for better clinical outcome and to prevent over-/underfeeding (Heidegger et al. 2013; McClave et al. 2014). Difficulties in conduct, handling and interpretation of results often limit the use of IC in ICU patients. IC is the method utilised to measure EE in patients both during mechanical ventilation (MV) and can also now be routinely used in patients not requiring MV. The need for accurate determination of EE is

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increasing due to the rising prevalence of patients with clinical conditions making traditional equation-based estimation of EE unpredictable and plagued with variability. For example, elderly subjects with reduced lean body mass and increased fat mass have a reduced EE, not easily predicted with traditional equations for caloric need. In contrast, young patients, those with severe trauma, acute infection or significant obesity can have increased EE that is also difficult to estimate without IC (Heidegger et al. 2013; McClave et al. 2014). A number of studies have shown that predictive formula developed to calculate EE of such patients are not consistently clinically relevant (Fraipont and Preiser 2013; Guttormsen and Pichard 2014). Indeed, clinicians need to measure their patients' EE in order to optimise the prescription of nutritional support and the clinical outcome (Heidegger et al. 2013; McClave et al. 2014), and IC is considered to be the gold standard for determining EE in the ICU patients. This is now becoming a reality with the development and ongoing evaluation of new, easy-to-use indirect calorimeter technology.

Conclusion: An Exciting New Era for Objective Malnutrition Diagnosis and Personalisation of Nutrition Delivery

The advent of a range of novel and innovative technologies to allow objective diagnosis of malnutrition, accurate determination of nutrition needs, and evaluation of nutrition utilisation is a major advance in the nutritional and metabolic care of critically patients. We believe it is essential that some or all of these devices are utilised in all future critical care nutrition trials to assess and guide malnutrition diagnosis and nutrition therapy. All of these devices continue to require further research to better evaluate their optimal application in ICU outcomes and care. Many of these trials are planned or underway. It is our dream that one day the muscle-specific ultrasound, the SBIS, and the new generation of metabolic carts will become to the ICU dietitian what the pulse oximeter, blood pressure cuff, and stethoscope are to the ICU nurse. We believe this will finally usher in an era of truly personalised nutrition care.

Conflict of Interest

Paul Wischmeyer reported receiving grant funding related to this work from National Institutes of Health, Canadian Institutes of Health Research, Nutricia, Abbott, Baxter, Fresenius, and Takeda. Dr. Wischmeyer has served as a consultant to Abbott, Fresenius, Baxter, Cardinal Health, Nutricia, and Takeda for research related to this work. Dr. Wischmeyer has received unrestricted gift donation for nutrition research from Musclesound and Cosmed. Dr. Wischmeyer has received honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter and Nutricia.

Jeroen Molinger has received grant funding related to this work from Nutricia and Baxter. He serves as consultant for Musclesound Inc. and Nutricia. ■

Key points

- ICU acquired weakness (ICU-AW) is a common complication of critical illness.
- An increasing number of patients who survive ICU suffer from severe, prolonged functional disabilities.
- Priority must be given to research addressing post-ICU QoL outcomes in survivors.
- One low-cost therapeutic strategy that can be rapidly implemented is objective, data guided personalised nutrition delivery to attempt to maintain and allow recovery of muscle mass/function.
- The use of a quick non-invasive technique to evaluate skeletal muscle quantity and quality in ICU patients could have profound prognostic implications for how malnutrition is diagnosed.

Abbreviations

ARF	Acute Renal Failure
ASMI	Appendicular Skeletal Muscle Index
BIA	Bioelectrical Impedance
ECW	Extracellular Water
EE	Energy Expenditure
FFM	Fat-Free Mass
GLIM	Global Leadership Initiative on Malnutrition
IC	Indirect Calorimetry
ICU	Intensive Care Unit
ICU-AW	ICU Acquired Weakness
ICW	Intracellular Water
IMAT	Intramuscular Adipose Tissue
IMGC	Intramuscular Glycogen Content
LBM	Lean Body Mass
MS	Muscle Size
MV	Mechanical Ventilation
REE	Resting Energy Expenditure
SBIS	Segmental Bioelectrical Impedence Spectroscopy
U/S	Ultrasound
QoL	Quality of Life

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NUTRITION IN THE ICU

NUTRITION – KEY FACTS

At least **one third** of patients in developed countries have some degree of malnutrition upon admission to the hospital.

If left untreated, approximately **two thirds** of those patients will experience a further decline in their nutrition status.

Among patients who are not malnourished upon admission, nearly **one third** may become malnourished while in the hospital.

According to the NutritionDay ICU Audit, it takes **1 week** to reach 1500kcal intake in most ICUs in the world.

Undernutrition is associated with **prolonged length** of stay, mechanical ventilation, infection and mortality.

Overnutrition is associated with **prolonged** mechanical ventilation and infection, and increased morbidity.

Source: Tappenden et al. (2013) Jrnl of the Acad. of Nutr. and Dietitics, 113(9); Singer (2019) Critical Care 23(1).

OBJECTIVES OF NUTRITION THERAPY IN THE ICU

- Preserve lead body mass
- Maintain immune function
- Avert metabolic complications

Source: VanBlarcom and McCoy (2018) Crit. Care Nurse, 38(3):46-52.

NUTRITION DISORDERS AND RELATED CONDITIONS

- ✓ Malnutrition/Undernutrition
- ✓ Sarcopenia/Frailty
- ✓ Overweight/Obesity
- ✓ Micronutrient abnormalities
- ✓ Refeeding syndrome

Source: Singer et al. (2019) Clinical Nutrition, 38:48-79.

NUTRITION CARE PROCESS

1. Nutrition Assessment
2. Nutrition Diagnosis
3. Nutrition Intervention
4. Nutrition Monitoring and Evaluation

Source: Cederholm T et al. (2017) Clin. Nutrition, 36:40-64.

KEY PRINCIPLES TO IMPROVE NUTRITION FOR THE CRITICALLY ILL

- Create a culture where all stakeholders value nutrition
- Redefine clinicians' roles to include nutrition care
- Recognise and diagnose malnourished patients and those at risk
- Implement comprehensive nutrition interventions and monitor continuously
- Communicate nutrition care plans
- Develop a discharge nutrition care and education plan

Source: Tappenden et al. (2013) Jrnl of the Acad. of Nutr. and Dietitics, 113(9).

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The Role of Speech and Language Therapy Supporting Nutritional Management in ICU

Speech and Language therapists have a supporting role in the nutritional management of ICU patients, from identifying dysphagia risk factors to facilitating oral intake and improving clinical outcomes.

Speech and Language Therapists (SLT) are recognised members of the multidisciplinary team working in the Intensive Care Unit (ICU), with a focus on the rehabilitation of communication and swallowing difficulties (oropharyngeal dysphagia). Patients who are admitted to the ICU are likely to need support for at least two organs and this may include ventilatory support necessitating a tracheostomy. A number of studies have identified a link between insertion of an artificial airway and disruption to laryngeal functions, which includes both voice and swallowing (Brodsky 2018). In the UK, the role of SLT extends to the optimal management of secretions, supporting the weaning process from assisted ventilation to self-ventilation through to decannulation as well as facilitating a return to oral intake (Royal College of Speech and Language Therapists 2014). A great deal of therapy intervention may be required prior to consideration of oral intake during which time a patient will require non-oral nutrition to support them through their rehabilitation.

Normal Swallowing

To better understand the disruption to swallowing, it is valuable to be familiar with the normal process of swallowing. This involves the precise coordination of reflexes and muscle movements across a three stage process (Groher and Crary 2015). At the oral stage, food or fluid is introduced into the mouth through the lips, then manipulated and controlled by the tongue to form a cohesive bolus that is then forced into the pharynx by the back of the tongue under pressure. This triggers the pharyngeal stage of swallowing leading to a series of biomechanical movements which raises and tilts the larynx to enable closure of the airway whilst simultaneously opening the oesophageal entrance (**Figure 1**). During the oesophageal stage the bolus transfers through the oesophagus to the stomach for further digestive processing (McRae 2018). Any disruption to the timing or range of movements at the oral or pharyngeal stage results in a risk of food or fluid entering the airway, with negative health consequences, such as chest infection and respiratory compromise. If food or fluid is not being absorbed into the digestive system, there is a loss of nutritional value which further compromises patients' immunity to fight infection.

> "pharyngeal dysfunction and dysphagia has been associated with muscle weakness in critically ill patients and linked to increased risk of aspiration, with poorer outcomes"

Causes of Oropharyngeal Dysphagia

As survivorship of patients increases in ICU, the awareness of the incidence of oropharyngeal dysphagia has also increased, due to its negative impact on mortality. Causes appear to be multi-factorial and include the primary diagnosis, especially neurological, respiratory interventions and ICU acquired weakness (Schefold et al. 2017). For this reason, it has been difficult to identify incidence with reports ranging from 3 to 62% (Skoretz et al. 2010).

Primary Diagnoses

A number of neurological disorders cause disruption to muscle strength and movement and interfere with normal swallowing. This includes stroke, progressive neurological disorders and traumatic brain injury. Infections and tumours in the oropharynx or nervous system can also cause disturbances to swallowing functions. Patients with neurological conditions in ICU are reported to require increased mechanical ventilation and extended lengths of stay with persisting dysphagia (Macht et al. 2013).

Respiratory Interventions

Many ICU patients will require an endotra-

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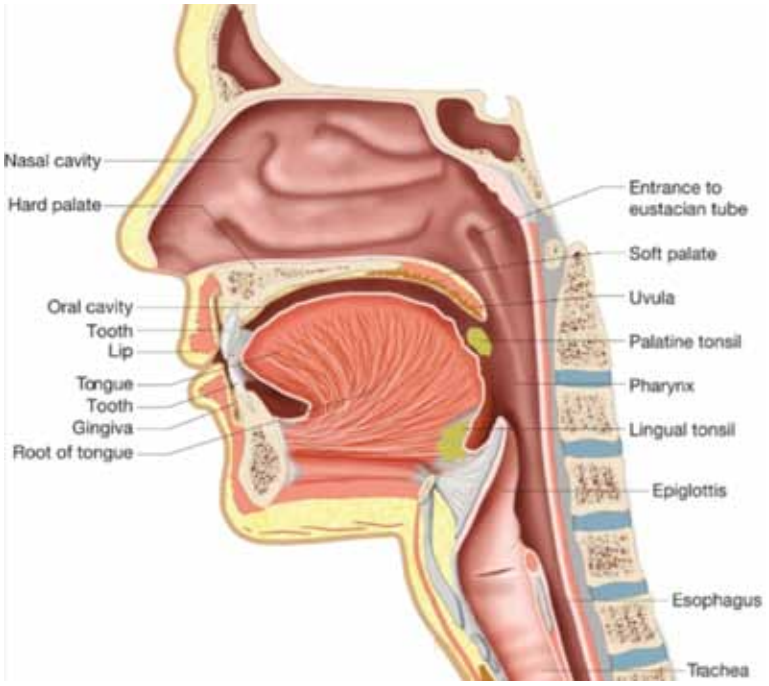

Figure 1. Cross section of head and neck anatomy - demonstrating close proximity of laryngeal opening to oesophagus

cheal tube or tracheostomy tube to assist ventilation during their admission. An increasing amount of evidence indicates that these can lead to mechanical and physiological disruption to laryngeal functions (Brodsky et al. 2018; Skoretz et al. 2010). This has been termed post-extubation dysphagia (PED) and is acknowledged as being a hidden condition with a high rate of silent aspiration, which demands early identification and intervention (Kwok et al. 2013; Perren et al. 2019).

ICU Acquired Weakness

This describes varying degrees of muscle weakness and atrophy that occurs in up to 80% of critical care patients, often due to immobilisation and disuse (Jolley et al. 2016). Pharyngeal dysfunction and dysphagia has been associated with muscle weakness in critically ill patients and linked to increased risk of aspiration, with poorer outcomes (Mirzakhani et al. 2013; Ponfick et al. 2015).

Regardless of cause, dysphagia has a negative impact on overall health status and mortality with higher healthcare costs (Altman et al. 2010). Despite increased awareness, routine swallow screening with a planned intervention is not standard practice in ICUs, but this may help to prevent symptoms of aspiration (Zuercher et al. 2019).

The Personal Impact of Dysphagia

It is important to consider the personal impact of not eating and drinking. Oral intake not only provides nutritional benefits but has psychological and emotional importance, adding significantly to quality of life (Barr and Schumacher 2003). Communal eating is often attached to family and social events, with many cultures using food and drink in celebration of life events. This needs to be a consideration in the clinical decision-making process, to ensure that social inclusion is maintained without compromise to health (Watson and Bell 2014). Studies have demonstrated the negative impact of not being able to eat that included shame, anxiety and dependence (Carlsson et al. 2004; Jacobsson et al. 2000; Larsen and Uhrenfeldt 2013). For patients in ICU, the process of resuming oral intake signifies recovery and a return to normality through reintegration into the daily routine of mealtimes and sharing food with friends and family (Segaran 2006). Consideration of the impact on quality of life is important when decisions are being made about long-term nutritional needs.

Clinical Management of Oropharyngeal Dysphagia

Recent UK guidance for critical care recommend that all tracheostomy patients are assessed by SLT as standard (Faculty of Intensive Care Medicine & Intensive Care Society 2019) although current levels of SLT staffing are unlikely to be able to achieve this. Instead, frontline staff, such as nurses, doctors and allied health professionals are expected to identify risk factors for dysphagia in order to expedite a referral to SLT for swallowing assessment.

Swallow Screening

A number of screening tools have been developed for early identification of dysphagia. The Water Swallow Test offers a quick assessment of aspiration by checking for overt signs of coughing or wet voice after taking sips of progressive amounts of water (Suiter & Leder 2008). For ICU patients, there remains a risk of false negative results in the event of silent aspiration so additional detailed SLT assessments may be required to verify clinical signs (Brodsky et al. 2016). Other screening tools employ a two-stage process, where staff first review a checklist of risk factors for dysphagia, if passed, the second stage allows water trials. Examples are the GuSS-ICU (Christensen and Trapl 2018) and the PEDS tool (Johnson et al. 2018) which allow early commencement of oral intake for those with no risk factors or dysphagia signs.

SLT Assessment

A swallow assessment by SLT will firstly involve a bedside evaluation to check range and strength of oral-motor movement, swallow timing, voice and cough. Gold standard instrumental assessments that support a definitive dysphagia diagnosis are Fibreoptic Endoscopic Evaluation of Swallowing (FEES) and Videofluoroscopy

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Figure 2. The IDDSI Framework and Descriptors. Licenced under Creative Commons

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(VFS). For patients restricted to ICU, FEES offers portability and can be undertaken at the bedside to directly view the functions of the pharynx and larynx for speech, breathing and swallowing tasks (Langmore 2001). In contrast, VFS is a video-x-ray that takes place in the radiology department, with the patient being given radio-opaque coated food and drink of varying textures which is then recorded and analysed for swallow timing, speed and effectiveness (Logemann 1998). Based on these assessments, an intervention plan can be developed to address specific swallowing impairments.

Dysphagia Management Options

Non-oral

If assessments show that swallowing function is unsafe for fluids or food consistencies and there is evidence of aspiration, the SLT may make a recommendation for the patient to remain nil by mouth in order to undertake a programme of therapy to rehabilitate the swallowing impairment. To maintain nutrition, the team would need to decide on short- or long-term options for enteral feeding which may be via a nasogastric (NGT) or gastrostomy tube. National guidance recommend that those with dysphagia should have a 2-4 week trial of nasogastric feeding prior to a team review to consider prognosis and future feeding requirements (National Collaborating Centre for Acute Care 2006). There has been evidence to suggest that NGT can disrupt swallow physiology (Pryor et al. 2014), so if dysphagia is likely to be prolonged, a percutaneous endoscopic gastrostomy should be considered (Dwyer et al. 2002). This is a reversible procedure, so that when oral intake resumes the tube can be removed.

Dry Mouth

A strong feature of the acute experience of many ICU patients is the feeling of a dry mouth and a strong desire to drink to achieve relief from thirst (Arai et al. 2013). Dry mouth is often a side effect of medication, reduced oral intake and mechanical ventilation (Kjeldsen et al. 2018; Stotts et al. 2015). A dry mouth and throat can make it difficult to swallow or talk but for those with dysphagia who need to be nil by mouth drinking poses a dilemma, as this may introduce a risk of aspiration. Regular mouthcare as well as oral moisturisation using artificial saliva products (McRae 2011) or a thirst care-bundle (Puntillo et al. 2014) can help to provide relief whilst minimising risk and improve wellbeing during acute care.

Swallow Therapy Interventions

The SLT may identify specific impairments that can still permit safe swallowing with diet modifications to minimise risk of aspiration. The International Dysphagia Diet Standardisation Initiative (IDDSI) provides a universal framework to describe food and fluid textures on a continuum of eight levels (**Figure 2**). Oral intake will need to be supervised and a food chart kept, to track both amount and consistency of food and drink taken so that informed decisions are made to upgrade or downgrade diet textures.

Alongside a modified diet, SLTs may recommend a range of swallow exercises or strategies to improve motor and sensory functions of the oropharyngeal system to improve swallow safety and return to normal diet (Martino and McCulloch 2016).

> consideration of the impact on quality of life is important when decisions are being made about long-term nutritional needs

Risk Feeding

In some instances, there may be a decision to continue oral diet that is at risk of being aspirated, if alternatives are not an option. This is termed 'risk-feeding' or Eating and Drinking with Acknowledged Risk (EDAR). This may be considered as an option for patients who have significant multi-system

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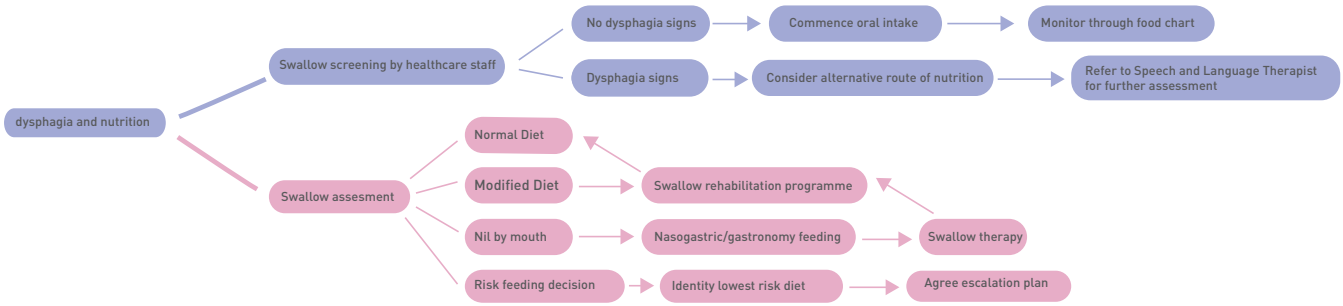

Figure 3. Flow diagram of clinical decisions for dysphagia and nutritional management

impairments with poor prognosis, and alternative methods of nutrition may be unsuitable or unsafe (Hansjee 2018). This requires discussion and documentation of decisions with staff, family members and the patient, if possible. The SLT's role will be to assess the patient's swallowing to ensure the most risk-free textures are provided. As a team it is crucial to achieve an agreement on the course of action in the event of clinical deterioration. Use of a decision tool (**Figure 3**) for those with complex dysphagia can ensure that patients experience less time being nil by mouth and a patient-centred approach to decision-making (Sommerville et al. 2019).

Outcome Measures

There are a number of outcome measures to evaluate progress in dysphagia rehabilitation. Some are used by SLTs with instrumental assessments to describe the degree of impairment, such as the Penetration Aspiration Scale (Rosenbek et al. 1996), the Secretion Severity Rating scale (Murray et al. 1996) and Yale Pharyngeal Residue Severity Rating scale (Neubauer et al. 2015). Patient reported outcome measures provide insight into the impact dysphagia on the person and environment. The Functional Oral Intake Scale (FOIS) is a seven-point scale that describes the degree of swallowing function and oral intake or tube feeding required (Crary et al. 2005). The Swallowing Quality of Life Questionnaire (SWAL QOL) (McHorney et al. 2002) is a 44 item self-rating scale that helps to describe dysphagia symptoms, whilst the Eating Assessment Tool (EAT-10) (Belafsky et al. 2008) is a shorter 10 item list for people to describe their dysphagia severity and monitor changes.

Conclusion

SLTs are an integral member of the multidisciplinary team and have a role in the decisions around oral intake and interventions that may be required for those with dysphagia who will have compromised nutritional intake. Early identification of risk factors and management of impairments can help to ensure nutrition is optimised so that patients can participate in rehabilitation to improve thier outcomes and quality of life. ■

Conflict of Interest

None.

Key points

- In the UK, the role of Speech and Language Therapists (SLT) extends to the optimal management of secretions, supporting the weaning process from assisted ventilation to self-ventilation through to decannulation as well as facilitating a return to oral intake.
- Recent UK guidance for critical care recommend that all tracheostomy patients are assessed by SLT as standard.
- SLTs are an integral member of the multidisciplinary team and have a role in the decisions around oral intake and interventions that may be required for those with dysphagia who will have compromised nutritional intake.

Abbreviations

EAT	Eating Assessment Tool
EDAR	Eating and Drinking with Acknowledged Risk
FEES	Fibreoptic Endoscopic Evaluation of Swallowing
FOIS	Functional Oral Intake Scale
ICU	Intensive Care Unit
IDDSI	International Dysphagia Diet Standardisation Initiative
NGT	Nasogastric
PED	Post-Extubation Dysphagia
SWAL QOL	Swallowing Quality of Life Questionnaire
SLT	Speech & Language Therapists
VFS	Videofluoroscopy

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Virtual Reality in the Intensive Care Unit: State of Play and Future Prospects

An overview of the practical uses of virtual reality in the ICU and the benefits it can provide.

One way of defining virtual reality (VR) is as the set of techniques and systems required for human beings to enter computer-generated synthetic worlds. VR techniques are based on real-time interaction with an artificial immersive world using behavioural interfaces that enable both physical and emotional perceptions of a number of sensations (including visual, auditory and haptic perception).

It is difficult to pinpoint the source of the concept of virtual reality. Indeed, as far back as antiquity Plato reflected, in the Allegory of the Cave (The Republic, Book VII), on the persuasive powers of images and their ability to deceive the senses. It was not until 1938 that the term virtual reality was published for the first time by the writer Antonin Artaud in The Theater and Its Double. In 1935 S. Weinbaum, the science-fiction author of Pygmalion's Spectacles, first depicted glasses bearing an uncanny resemblance to modern-day VR headsets (allowing the wearer to experience a fictional world through holograms, smell, taste and touch).

From a technical perspective, the ancestor of virtual reality dates back to the mid-19th century and the invention of the first stereoscopes that were able to generate three-dimensional photographs from two-dimensional images. In 1957, Morton Helling invented the first immersive cinema (the Sensorama simulator), enabling immersion in short films by harnessing a range of senses (using stereo sound, vibrating seats, smell diffusion, and fans).

The first VR headset dates back to 1968 and featured the Sword of Damocles (Ivan Sutherland). But it was not until the 1980s that the VR experience became more widely available via Jaron Lanier, using more ergonomic headsets and gloves (the DataGlove) that provided total immersion. Since then, NASA, the armed forces and the video game industry have been contributing to a significant evolution in VR technology for industrial and commercial use.

The scope of activity of VR has broadened since the early 2000s. This technology is widely employed in many sectors such as law, architecture, communication and industrial design.

One of the first ideas behind VR applied to the medical field comes from Eccleston et al. in 1999 and their work on pain's cognitive modulation through attention, which was strengthened by Bantick et al. in 2002 with their original study using functional MRI to assess those neurocognitive changes.

Since then the scientific literature has become increasingly extensive, encompassing cognitive behavioural therapies in psychiatry and addiction care, the effects of VR on pain pathways and anxiolysis in pain management and palliative care, surgeon training in surgery, Parkinson's patients in neurology, physical therapy, and alongside locoregional anaesthesia or simply when anaesthesia is administered in anaesthesiology.

Recently its applications have developed to reach biofeedback therapies and preventing pain catastrophisation in chronic pain. In 2018 a meta-analysis by Chan et al. (2018) pointed a beneficial effect for VR versus control groups in 16 well conducted randomised controlled trials with analgesia as their primary outcome, including various medical units.

What are the implications for intensive care medicine in 2019? The literature is unfortunately rather sparse. And yet the scope for VR in intensive care is, in our view, considerable.

Patients admitted in the intensive care unit are subjected to a multitude of unpleasant sounds, lights and nociceptive pain which can be perceived as a hostile environment. They predominantly recount feelings of anxiety and discomfort generated by both an unfamiliar and stressful surrounding and numerous care-related procedures that are liable to induce cognitive dysfunction accounting for delirium in up to 31% of cases (Aruguman et al. 2017), post-intensive care syndrome in between 17% and 43% (Needham et al. 2013; Pandharipande 2013; Davydow et al. 2013) of cases and post-traumatic stress disorder in between 15% and 40% (Righy et al. 2019) of cases according to scientific studies. These

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complications are known to be associated with an increase of the average length of hospital stay, morbidity and mortality.

Turon et al. (2017) investigated the use of VR and its safety using a system comprising a television screen and a motion sensor for patient interaction. The results seem promising since it showed that critically ill patients mostly considered the sessions enjoyable and relaxing without being overly fatiguing.

The use of VR in intensive care units is ostensibly beneficial in reducing anxiety by immersing patients in a soothing, comforting environment. It could potentially be employed in critical patients to help tolerate mechanical ventilation, enhance physical therapy to combat sarcopenia and exert an anxiolytic and analgesic effect during painful procedures (catheter insertion, painful dressing changes, or progressive drain removal). Moreover, it can be a determining tool in restoring the patient's sense of purpose in the healing process.

In our view, it is of interest to assess the feasibility of using a VR headset to intensify the degree of patient immersion within this context.

Standardised protocols are therefore required to undertake feasibility and safety studies of VR headsets to determine their use and efficacy in intensive care units. Regarding feasibility, use of VR headsets should be assessed in terms of accessibility to this technology (purchase price and maintenance), ease of bedside installation, training of the care team and implications for healthcare.

In terms of safety, we believe it is important to catalogue any significant adverse effects that may arise from a session. These may be neurocognitive (delirium, anxiety, agitation) or physical (nausea/vomiting, removal or displacement of medical devices, incidence of falls or trauma). Furthermore, it is important to assess tolerance since the headset involves not only visual but auditory isolation. In our view the risk of cross infection between patients should also be assessed since it could be seen as a drawback (assessment of disposable sanitary eye masks and headset disinfection procedures).

At the dawn of a constantly evolving technology and an increase access to affordable devices that can become of everyday usage, it seems legit to focus on the practical uses of Virtual Reality in the ICU and the benefits it can provide. Given that the literature on this topic is quite sparse, further clinical studies are required to assess the efficacy of using this type of technology, knowing that it can be hard to assess some minor changes in the above-mentioned criteria. ■

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Pre-packed Critical Care Drug Pouch for Acute Patient Care: Consensus, Simulation Testing and Recommendations

Human factors are significant contributors to drug error. To overcome some of these human factors, we propose standardisation and consolidation of agreed drugs and equipment into a compact pre-packed critical care drug pouch (CCP) for use in non-theatre environments.

Introduction

Emergency and sedation drugs availability and preparation represent a challenge in the setting of acute care or resuscitation outside the intensive care unit [ICU] (Glavin 2010; Sakaguchi et al. 2008) (**Figure 1**). Webster et al (2001) identified an error rate as high as 1 in 133 routine anaesthetics with root causes being syringe swaps (20%) and incorrect doses due to human errors (20%). More stressful environments such as the acute care settings have an even greater risk of preventable errors (i.e. avoidable by any means currently available), reaching 30% (Wilmer et al. 2010).

On the contrary, Highly Reliable Organisations (HROs) have the capacity to operate in hazardous situations with consistent, effective, nearly failure free performance, whilst maintaining optimum output (Roberts 1990; La Porte 1996). HROs encourage the use of checklists and pre-packed equipment to reduce variability and errors caused by human factors. There is substantial material published about the ideal content of cardiac arrest trolleys, difficult airway trolleys, and transfer equipment bags (Henderson et al. 2004). Unfortunately, there is little in the literature about the drugs available and desirable during a critical care transfer or emergency intubations outside the ICU. The aim of this project is to illustrate the process used for defining the content through to implementation of a critical care pre-packed resuscitation pouch (CCP).

Methods

A pre-packed "Critical Care Drug Pouch" has been recently introduced in a large London metropolitan hospital. There was no pre-defined standard against which to compare preceding this project. A modified two-round Delphi and Nominal Group method was used to achieve consensus throughout the project as illustrated in **Figure 2** (Hasson et al. 2000; Foth et al. 2016). The project was registered as a quality improvement activity by the Hospital Trust and interviews were anonymously conducted only with the staff working in the ICU. Quality improvement projects in the United Kingdom (UK) do not require ethical approval as soon as these are approved by the audit lead and the division leads as there was no direct patient interaction.

The project was divided into a two-round consensus study beginning with a nominal group session followed by the first round of a Delphi approach using electronic questionnaires. These results were further voted upon by the nominal group and a second round of Delphi performed via simulation and implementation to acquire further feedback and consensus. This nominal group (NG) consisted of a range of 4 experts deemed by seniority and experience: Intensive Care consultant, Practice Improvement Lead Nurse, 2 Senior Anaesthetic registrars (who frequently assisted in, or performed emergency intubations on ICU and within the hospital).

Nominal Group Review 1

An initial face-to-face brainstorm was performed by the NG after briefing on the

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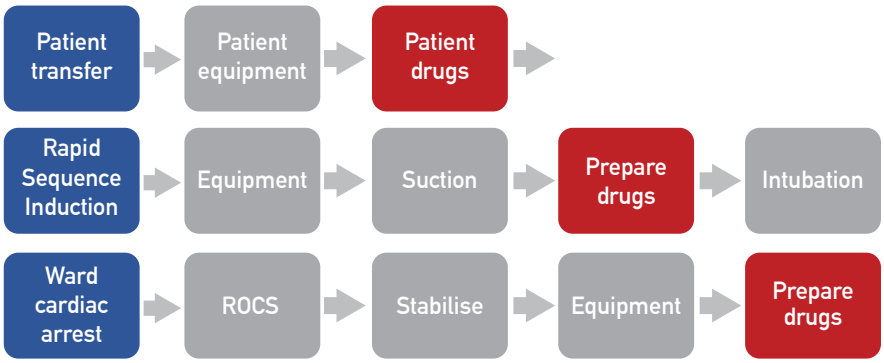

Figure 1. Scenarios requiring preparation of drugs in critical care situation. In several common critical care episodes, the preparation of drugs is time consuming and a rate limiting step.

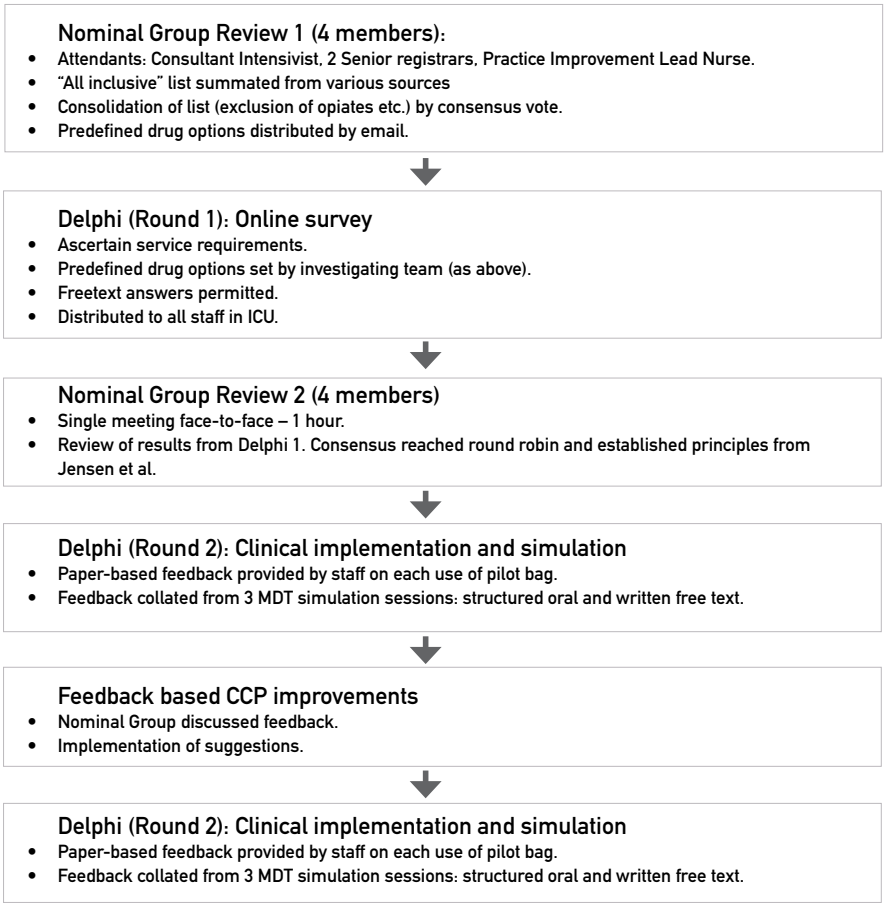

Figure 2. Methods - A two-round modified Delphi method was used alongside simultaneous nominal group method to achieve consensus for the project.

project aims over 1 hour. Questions were determined to ask the Delphi group to ascertain feasibility and necessity for the critical care drug pouch. An initial all-inclusive list of drugs was compiled from established models used in advanced life support (ALS) and ambulance service (Wijesuriya and Brand 2014) (eastamb.nhs.uk/policy-libraries/drugs-matrix/274; resus.org.uk/quality-standards/acute-care-equipment-and-drug-lists/; e-lfh.org.uk/e-learning-sessions/rcoa-novice/content/started/theatre.html). The NG excluded "controlled-drugs" such as opiates due to clinical governance constraints. Delphi group respondents were presented with a list of drugs (**Table 1**) plus a free text option to provide further input (drugs/contents).

Delphi (Round 1): Online Survey

A single-site pre-implementation online survey was conducted following the NG meeting to understand the needs of the end-user groups. The survey link was distributed via email to the doctors and nurses of the ICU team, introducing the aims of the project. Responses were collated over a two-week period with a second round of emails sent after the first week to improve response rate. The survey link contained an in-built validation field to ensure repeated answer by the same user did not occur. Respondents were kept anonymous. The questionnaire was composed of two main parts namely part one questions needed to understand the clinical requirement for the bag and the second to illicit choice of drugs for the CCP as described above. The survey collected also data related to demographic information (role and seniority) and seniority (experience) of respondents.

Nominal Group Review 2

The results of Delphi round 1 were reviewed by the same NG of experts prior to a scheduled 1 hour face-to-face meeting. Pre-defined principles to reduced medication error from Jensen et al. (2014) were applied to determine the contents and form of the prototype CCP. Ideas were shared in a round-robin fashion followed by group discussion. A list of priority drugs was established based on the multiple choice and free text answers from Delphi round 1, and drugs were selected with appropriate support materials.

Delphi (Round 2): Clinical Implementation and Simulation

A prototype pouch bag was prepared in collaboration with the hospital pharmacy containing the drugs and required equipment. Following implementation, feedback was gathered from end-users from two sources:

1. Questionnaires following clinical use during the first 4 weeks of implementation.
2. Verbal and written feedback following

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Wijesuriya et al. (2014)	East of England Ambulance Service Drug Matrix	Resuscitation Council UK- ALS
Suxamethonium 100mg	Gluco gel (hypostop) 40%	Adenosine 6 mg x 5
Atracurium 50mg	Adrenaline pre-filled	Atropine - 1mg x 3
Atropine 600mcg	Adrenaline injection	Adrenaline 1mg (= 10 ml 1:10,000) prefilled syringe
Glycopyrollate 200mcg	Glucagon injection	Amiodarone 300mg x 1
Neostigmine 2.5mg	Ipratropium bromide inhaler (nebuliser soln)	Calcium chloride 10 ml 10% x 1
Metaraminol 1mg	Naloxone injection	Chlorphenamine 10 mg x 2
Phenylephrine 10mg	Nitrolingual aerosol spray	Hydrocortisone 100 mg x 2
Metoprolol 5mg	Salbutamol nebules	Glucose for intravenous use
Amiodorone 150mg	Amiodarone injection	20% lipid emulsion 500 ml
Thiopentone 500mg	Atropine sulphate minijet	Lidocaine 100 mg x 1
Propofol 200mg 1%	Benzylpenicillin injection	Magnesium sulphate (2 g = 8 mmol) x 1
Etomidate 20mg	Chlorphenamine injection	Midazolam 5 mg in 5 ml x 1
Rocuronium 50mg	Furosemide injection	Naloxone 400 microgram x 5
Adenosine 6mg	Glucose infusion	Potassium chloride
Magnesium 5g	Hydrocortisone injection 100mg/ml	Sodium bicarbonate 8.4% or 1.26%
Calcium Chloride 10mmols	Ondansetron injection 4mg/2ml 5	Adrenaline 1mg (1 ml 1:1000)
Ephedrine minijet	Paracetamol injection	Aspirin 300 mg and other antithrombotic agents
Atropine minijet	Sodium chloride infusion 0.90% 500ml	Furosemide 50 mg IV x 2
Adrenaline minijet	Tranexamic acid	Flumazenil 0.5 mg IV x 2
Propofol 1% for infusion	Water for injection 20x10ml	Glucagon 1 mg IV x 1
	Lidocaine 2% injection	GTN spray
	Tetracaine	Ipratropium bromide 500 mcg nebules
	Dexamethasone 2mg/5ml 10ml	Salbutamol 5mg nebules x 2
	Hyoscine butylbromide 20mg/1ml	0.9% sodium chloride or Hartmann's solution
	Lidocaine 1% injection 50mg/5ml 20x5ml	Adrenaline 1mg 1:10,000 minijet
	Prochlorperazine injection 12.5mg/1ml 10	Amiodarone 300mg minijet
	Salbutamol inhaler TTA pack 100mcg Each	
	Aciclovir injection 500mg/20ml 5	
	Adenosine injection 6mg/2ml 6	
	Calcium chloride 10% injection 10ml 1	
	Ceftriaxone injection 1g 1	
	Co-Amoxiclav injection 1.2g 1	
	Cyclizine 50mg/1ml 5x1ml	
	Dexamethasone injection 6.6 mg/2ml 5	
	Enoxaparin injection 120mg/0.8ml 1	
	Ephedrine injection 30mg/10ml 1	
	Etomidate injection 20mg/10ml 10	
	Flumazenil injection 500mcg/5ml 1	
	Haloperidol 5ml/1ml 5x1ml	
	Hartmanns infusion 500ml	
	Lidocaine 1% w/v 100mg/10ml 1	
	Metaraminol 10mg/1ml 10x10ml	
	Metoprolol injection 5mg/5ml 5	
	Phenytoin injection 250mg/5ml 1	
	Propofol injection 200mg/20ml 5	
	Propofol 1% 10mg/1ml 50ml bottle	
	Rocuronium injection 50mg/5ml 10	
	Sodium bicarbonate 50mmol/50ml 1	
	Sodium bicarbonate 8.4% (1 mmol/ml) 50ml	

Table 1. Comparison of drug inventories from Wijesuriya et al. (2014) (Remote airway management bag), East of England Ambulance Drug Matrix, Resuscitation Council UK ALS guidance.

integration of the CCP into 3 multidisciplinary clinical simulation sessions conducted over a 2 week period.

Written questionnaires were attached to the storage unit of the CCP to permit feedback after each clinical use. Respondents were presented with multiple choice questions on whether or not their experience of drug preparation in critical care was made more efficient, quicker and easier. Free text was also permitted to allow suggestions. Questionnaires remained anonymous. Participants were allowed to respond multiple times given that they may use the bag in different clinical scenarios separated in time and place. This permitted real-time feedback regarding the use of the bag at each use to ascertain safety and functionality issues.

The bag was also incorporated into 3 of the regular multi-disciplinary clinical simulation sessions to troubleshoot problems regarding function and to increase awareness. Feedback was requested verbally and as part of the session feedback in the simulator. This second round of the modified Delphi method allowed the same large end-user group to reach further consensus from real-time experience on useful amendments to be made to the bag.

Feedback Based CCP Improvements

The NG reconvened to review the results of feedback from the clinician questionnaires and from the simulation sessions. Practicality of suggestions were reviewed again using the summary of recommendations from Jensen et al. (2019) to prevent medical errors (**Table 5**) and restrictions set out by clinical governance and the storage of opiates. This resulted in a final complete CCP which is now in established practice.

Results

Nominal Group Review 1 Results

The initial NG review produced an all-inclusive list of drugs from sources as described. Oral tablets, rectal suppositories and enemas are

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Condensed option list presented to participants of Round 1:
Atropine
Ephedrine
Suxamethonium
Glycopyrollate
Propofol
Thiopentone
Rocuronium
Metaraminol
Omitted Drugs: Easy availability on ward
Adenosine, Adrenaline autoinjector, Amiodorone, Aspirin, Atracurium, Dextrose, Dopamine, Etomidate, Glucagon, GTN, Hydroxycobalamin, Ibuprofen, Ipratropium, Lidocaine, Magnesium, Methylprednisolone, Metoprolol, Naloxone, Neostigmine, Ondansetron, Paracetamol, Phenylephrine, Salbutamol nebuliser, Sodium Bicarbonate, Tranexamic Acid
Omitted Drugs: "Controlled Drugs"
Diazepam, Fentanyl, Morphine, Ketamine, Midazolam

Table 2. Condensed Drug options for the proposed CCP

Role on ICU	*n*	
Band 5 nurse	3	
Band 6 nurse or higher	9	
Senior House Officer	6	
Registrar	4	
Consultant	3	
Total	**25**	
	Yes	*No*
Have delays in drawing up medications previously affected the safety or care of patients?	24	0
Is the current set of medications sufficient for an emergency intubation?	15	7
Do you think the proposed bag will improve the experience of an emergency intubation?	23	1
Are you confident in correctly preparing drugs for an emergency intubation?	10	14
Was it easy to prepare equipment and drugs for the emergency intubation?		
Easy to prepare both	4	
Equipment easy but medications hard	6	
Medications easy, equipment hard	1	
Difficult in both	13	

Table 3. Results from Delphi round 1 online web-based questionnaire.

Would you want the following drugs in the CCP?		
	Yes	No
Atropine	13	11
Ephedrine	15	9
Suxamethonium	23	1
Glycopyrollate	23	1
Propofol	23	1
Thiopentone	5	19
Rocuronium	23	1
Metaraminol	22	2
Other suggested drugs: Adrenaline, Steroid, Salbutamol, Labetalol, Bag of normal saline, Atracurium, Ketamine, Thiopentone, Noradrenaline		

Table 4: Delphi Round 1 consensus options on drugs for the CCP.

Consensus for equipment and drugs to be kept in CCP		
	Yes	No
Atropine	13	11
Ephedrine	15	9
Suxamethonium	23	1
Glycopyrollate	23	1
Propofol	23	1
Thiopentone	5	19
Rocuronium	23	1
Metaraminol	22	2
Other suggested drugs: Adrenaline, Steroid, Salbutamol, Labetalol, Bag of normal saline, Atracurium, Ketamine, Thiopentone, Noradrenaline, MIdazolam		

Table 5. Results of Nominal Group Review 2

removed from the list for the sake of brevity. Drugs unrelated to critical care have also been removed. The remaining all-inclusive list is demonstrated in **Table 1**. By discussion the NG consensus led to removing large bags of intravenous fluids to ensure the CCP would be compact. Drugs which were easily available on the local wards and existing resuscitation trolleys were eliminated, therein nebulisers and antibiotics excluded. We described previously the constraints from clinical governance regarding the storage of controlled drugs such as opiates, ketamine and midazolam would not be permissible in an unsupervised clinical area. **Table 2** demonstrates the list of drug options presented to the participants via the web link questionnaire for Delphi round 1.

Delphi Round 1 Results

In the local pre-implementation questionnaire survey, 25 responses were received from 45 recipients following two email notifications containing the web link (3 Consultants, 3 Specialist registrars, 6 Senior House Officers, 12 ICU nurses) (**Table 3**). Only 1 respondent failed to complete all elements; their responses have been omitted from the analysis. There was a uniform agreement amongst responders that drawing up drugs for emergency rapid sequence induction and transfer was subject to errors and delays, and a significant proportion (32%) felt that the currently available drugs were insufficient for delivery of optimal care. The consensus opinion felt delays were present in finding both equipment and medications with potential patient compromise, and 96% of respondents felt that the drug pouch would improve this experience. Respondents felt that their knowledge of the drugs required for intubation was incomplete. **Table 4** demonstrates which drugs from the reduced list respondents felt were vital. Frequent mentions were seen for additional agents in the free text box: adrenaline, atracurium, ketamine, thiopentone, noradrenaline.

Nominal Group Review 2

The same nominal group reviewed the results of the first Delphi round. A consensus was obtained that the pouch should be minimalistic in size and contents, to permit easy and mobile use, daily check and reduction of waste. It was agreed that it should be in keeping with infection control guidelines and have clinical governance procedures in place to ensure sustained quality and safety.

The resulting pouch contains the minimum syringes (akin to routine anaesthetic practice) and drawing up needles. It was agreed that colour coded syringe labels would be contained in harmony with UK regulations and common anaesthetic practice as per the Association of Anaesthetist of Great Britain and Ireland guidelines to prevent "wrong

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Equipment		Stickers	
20mLs syringe	x3	Atropine	x2
10mLs syringe	x2	Ephedrine	x2
5mLs syringe	x2	Fentanyl	x2
2mLs syringe	x4	Glycopyrollate	x2
Drawing up needles	x4	Metaraminol	x2
		Midazolam	x2
		Propofol	x2
		Rocuronium	x2
		Suxamethonium	x2
		Blank	x2

Intubation medications	
Atropine	1mg x 3
Ephedrine	30mg x 1
Glycopyrollate	600micrograms x 1
Metaraminol	10mg x 1
Midazolam	10mg x 1
Propofol	200mg x 1
Rocuronium	50mg x 2
Suxamethonium	100mg x 1

Figure 3. (a): Closed bag. Dimensions 20 x 25 x 7cm. Wipe clean material. (b) Contents of open bags: drugs, syringes and needles held by elasticated bands. (c) Concise inventory attached to each critical care pouch.

drug" administration (Woodcock 2014). To facilitate standardisation, two small bags (20cm x 20cm x 7cm) with elasticated vial and mini-jet compartments, were introduced across the 25-bedded unit. The bag also contained a fixed inventory and audit form permitting accountability and ease of daily check. The expert consensus panel agreed from review of the pre-implementation questionnaire and free-text suggestions, that the bag should contain sedatives, hypnotics, neuromuscular blockade, inotropic and chronotropic agents to facilitate emergency intubation on the ICU/remote location or stabilisation of a patient prior to transfer. A diagrammatic/photographic representation of the layout, contents and inventory is provided (**Figure 3**). The pilot bag contained the following agents as per the consolidation of consensus reached: atropine, ephedrine, glycopyrollate, metaraminol, propofol, rocuronium, suxamethonium, adrenaline, and noradrenaline.

Delphi Round 2 Results

Multidisciplinary clinical simulation sessions provided positive feedback and in which staff felt that the speed of drug preparation was increased with chances of errors reduced, permitting a greater bandwidth for team focus on the clinical situation. Specifically, staff requested a crib sheet detailing the drug dilutions and syringe sizes pertinent to each drug to improve error prevention. Overwhelmingly, respondents felt that a drug bag with a quick reference guide would improve clinical care and that an associated simulation session would be beneficial. Nurses (n=5) and doctors (n=10) who completed the questionnaire following a real clinical episode unanimously felt that the new bag permitted:

a) Greater efficiency in sourcing necessary medications
b) Quicker commencement of the procedure/transfer
c) Contained all medications and equipment required

Free-text answers once again saw suggestions for additional drugs as mentioned previously. In particular midazolam, fentanyl and ketamine were identified. Thiopentone, adrenaline and atracurium were requested by one respondent.

Feedback Based CCP Improvements

Midazolam was added to the bag in subsequent iterations as this was not classified as a controlled drug on the unit. Adrenaline and thiopentone were also added as requested. Ketamine and fentanyl, though deemed desirable by many respondents, would require impractical layers of bureaucracy, reducing the bag's accessibility in an emergency. Atracurium was deemed unnecessary as this would not permit a safe emergency intubation, given the lack of a reliable reversal agent at the time of writing. As requested, a "dilutions and brief instructional crib sheet" was laminated and attached to each bag.

Discussion

The concept of a "pre-packed drug pouch" is needed for enhancing standardisation and creating a single set containing all necessary drugs and devices. This initiative was started in order to reduce errors and improve patient safety. The preparation of these drugs is time consuming and can often mean the loss of your best team members (critical care nurse, anaesthetic nurse, trainee doctors) whilst they retrieve syringes, needles, drug vials and labels from various locations. The CCP consolidates this search to one place.

Paramedic services and military experience have established practices for delivering acute care to patients in remote, unpredictable and stressful environments (Swinton et al. 2018; Burgess et al. 2018; Woolley et al. 2017). These professions deliver critical care to patients in remote, unpredictable and stressful environments and the presence of pre-packed systematic drug bags provide a portable, systems-based approach. The drug bags are standardised

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SUMMARY OF RECOMMENDATIONS EMPLOYED BY THE CCP
The label on any drug ampoule or syringe should be carefully read before a drug is drawn up or injected
Legibility and contents of labels on ampoules and syringes should be optimised according to agreed standards in respect of some or all of font, size, color and the information included (NB, there may be some disagreement on the detail of how this should be achieved).
Syringes should be labelled (always or almost always)
Management of inventory should focus on minimising the risk of drug errors
Syringes should be presented in prefilled syringes (where possible) rather than ampoules (either for emergency drugs or in general).
Colour coding by class if drug according to an agreed national or international standard should be used – of the syringe, part of the syringe, or of the syringe or ampoule labels

Table 6. Adaptation of recommendations by Jensen et al. 2004

and minimalistic allowing the right drug to be found and prepared quickly and marked clearly. The presence of pre-packed systematic drug bags provides a portable, systems-based approach (nwas.nhs.uk/media/950397/foi-263-web-response.pdf). The drug bags are standardised and minimalistic to easily allow the right drug to be found and drawn up quickly.

"To err is human" and studies have shown that the rate of drug related error is independent of clinician experience (Llewellyn et al. 2009). The solution is cheap, considering that studies show that the additional costs of medication errors can result in an extra $347 (Jiang et al. 2008) to $6647 (Nuckols et al. 2008) per patient secondary to medico-legal costs and increased bed-stay. Similarly Bates et al (1997) found an average increase of hospital costs by $4700 per admission or about $2.7 million annually for a 700 bed hospital as a result of medication errors (Bates et al. 1997). This is in comparison to the total cost of implementation of single bag and its contents: £86.00.

Several techniques to reduce errors attributable to wrong syringe, wrong dilution, wrong dose or wrong medication have been described by Glavin (2010) which emphasise standardisation and minimisation. Many of these are simple behavioural or visual aids and these have been incorporated into the proposed CCP.

Jensen et al. (2004) lays out 12 recommendations to develop systems and associated culture to reduce drug error and evidence based solutions. We share our implementation of these recommendations to reduce errors in preparation and delivery of drugs in our critical care unit (**Table 6**).

Limitations

Our study has several limitations:

1. The Critical Care pouch must be useful and cannot carry controlled drugs such as opioids.
2. Clinician's choice will vary. But a minimalistic principle was agreed and thus a common inventory generated: containing essentials for management of life-threatening emergencies and offer time to find more sophisticated solutions for the clinician's needs.

Following feedback, a clear learning curve was identified. 37% of staff felt they had some knowledge in drug preparation and 13% felt they were unable to prepare the drugs. Further multidisciplinary simulation training was implemented to overcome this alongside inclusion of the CCP in the induction of new staff and also crib sheets held within the bag to assist unfamiliar staff with the correct syringes and dilutions.

Overall the aim of the project is the reduction of potential errors secondary to human factors. It achieves this through several avenues:

1. Avoid the sourcing of drugs, syringes and labels from various locations in a time of emergency- often resulting in the loss of a valuable team member.
2. Portable solution to drugs required for intubation, stabilisation and transfer on the ICU or a remote location.
3. Clear, concise and colour coded labelling of syringes in harmony with existing anaesthetic practice, with guaranteed legibility.

Conclusion

The implementation of the Critical Care Pouch (CCP) demonstrates a patient-centred, safe, effective and sustainable remedy to reduce staff anxiety during preparation of emergency drugs during common and high stress situations in critical care environments. This successful pilot project was achieved through multiple systematic rounds of large (end user) and small (expert) groups of consensus using the modified Delphi method and nominal group technique. Its clinical success warrants further expansion to a regional level to reach consensus on a standardised bag with potentially greater impact on patient safety by reduction of drug administration errors and streamlined organisation. Progress has been made to create a complement to the already successful Critical Care Equipment Transfer bags established across the Northwest London Critical Care Network (Van Zwanenberg et al. 2016). ■

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For full review of contents of the bag and clinical governance please contact the critical care department at Charing Cross Hospital.

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Knowledge Transfer to Improve Outcomes in Critically Ill Immunocompromised Patients

An overview on sharing information, improving clinician skills, and transferring knowledge to ICU specialists about the care of immunocompromised patients.

Background

Studies have reported a volume-outcome relationship for cancer patients admitted to the ICU. In acute respiratory failure, mortality in ICUs managing more than 2 patients per week was 35%, whereas mortality is 70% in ICUs managing less than 1 patient per week (Lecuyer et al. 2008). The difference cannot be ascribable to benefits from being in a cancer hospital. In a large study from Brazil, the orchestra investigators reported that major differences were related to training programmes in critical care, daily visit of the oncologist in the ICU, presence of a clinical pharmacist and availability of protocols (Soares et al. 2016). Hence, educating ICU clinicians to improve their clinical skills remains a major endeavour.

Research Groups to Gather Data and Transfer Knowledge About the Care of Cancer Patients

The *Groupe de Recherche en Réanimation Respiratoire chez les patients d'OncoHématologie* (GRRR-OH) is a group of 32 centres in France and Belgium. Since 2003, this group has performed several cohort studies and clinical trials, mostly about acute respiratory failure in immunocompromised patients. In 2015, worldwide experts from 16 countries (Europe, USA, Canada, Brazil, Uruguay) established another research network named the Nine-I focusing more broadly on all immunocompromised patients, with special emphasis on cancer patients. Major research domains include i) diagnostic and therapeutic strategy in cancer patients (bronchoscopy vs. noninvasive diagnostic tests in acute respiratory failure, oxygenation and ventilation managements, steroids in pneumocystis pneumonia, aminoglycosides in patients with febrile neutropaenia and sepsis, acute kidney injury, empirical antifungals, management of CAR T-cells and immunotherapy-related related toxicity), ii) addressing the issue of undetermined ARF aetiology, iii) transfusion policies in sepsis, iv) de-escalation of anti-infectious agents and antibiotic stewardship, as well as v) clinical management of patients with nonmalignant haematological diseases (thrombotic microangiopathies, systemic vasculitis, and connective tissue diseases, emergency plasma exchange) (Mariotte et al. 2016). Main publications include studies in high impact factor journals in all the above-mentioned domains.

Current Opportunities to Transfer Knowledge About Immunocompromised Patients

The GRRR-OH organises 3 meetings per year and a 12-day course in French at the Paris University. These meetings combine formal lectures with open debates and controversies about the management of critically ill immunocompromised patients. Research ideas are also presented and discussed. Centres are invited to take part in these studies. The 12-day meeting (*Diplome d'Université*) includes one day per type of immune deficiency, including HIV-infected patients that are otherwise not included in our studies.

The Nine-I sets up a 1.5 day meeting in Paris at the end of March. Working groups prepare expert statements and position papers on different aspects of the care of immunocompromised patients. Then, formal lectures, controversies, and research ideas are discussed with all the group. In 2020, this meeting will be open to a wider public (March 30 and 31, 2020). From this group, an initiative focusing on CAR T cells related toxicity has been organised. Dr. Metaxa has hosted about 100 delegates in London in June 2019. Along this line, there will be another similar gathering of clinical data on patients admitted to the ICU following CAR T cell infusion (CARTTAS study - recruitment currently ongoing).

The Blood Diseases In The ICU (BDI) Training Course

Last year, we performed the first BDI course in St-Louis hospital, Paris. Thirty-six delegates attended this 5-day training course that covered most of the malignant and non-malignant haematological diseases. Interna-

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tional speakers came from Europe, USA and Brazil to give lectures to the participants. A limited number of delegates were welcomed to maintain a friendly ambiance, quality interactions, and opportunities to share experience, raise concerns, and ask questions. A social programme was also part of the course. The course will again be organised in 2020, from January 6-10. Registrations will be possible by email or through www.blood-diseases-icu.com.

The GRRR-OH Basic Functioning

Our study group has several elements of functioning that could be summarised in the five following domains:

1. **Strong Clinical Skills:** Every GRRR-OH member is recognised as a clinical leader for the care of critically ill immunocompromised patients, and may have expertise in a specific field of critical care. Acute respiratory failure remains the leading domain of interest. However, as the GRRR-OH grew up and evolved, themes such as acute kidney injury, sepsis, antibiotic stewardship, invasive fungal infections, and transfusion have broadened the research domains.
2. **Multidisciplinary Management:** Our ICUs follow the model of closed ICUs, led by independent and autonomous medical teams. We have accumulated experience in severe forms of critical care illness that complicates haematological malignancies and solid tumours (e.g. leukostasis, leukaemic infiltration, tumour lysis syndrome, urgent need for chemotherapy, as well as complications of CAR-T cell therapy and immunotherapy for solid tumours). We work closely with haematologists and oncologists. By managing numerous critically ill onco-haematological patients in the ICU, we have learned how to address patient needs and provide them specialised care. A daily discussion with haematologists and oncologists is the rule for every patient. Patients and relatives are informed by the two teams and treatment plans as well as the goals of care are set up with patients and families by the two teams on a daily basis. Along this line, residents and fellows from both specialties are trained in both haematology/oncology and critical care.
3. **A Fine-Tuned Organisation at the St-Louis Hospital, but Multiple Leaderships:** The GRRR-OH benefits from an organisation completely driven from St-Louis Hospital in Paris. All the administrative and organisational aspects are set up there. However, clinical and scientific leaderships are fairly distributed and shared across the GRRR-OH leaders. There is no doubt that our force is the sum of our expertise. For instance, each of us applies independently to various grants to fund studies, on behalf of the entire group. The GRRR-OH has a scientific advisory board, with each an expert in his own field of expertise.
4. **Transfer of Knowledge:** The GRRR-OH is a research group that has a large interest in transferring and acquiring knowledge. Besides the training courses listed above, every day advice is sought among the GRRR-OH experts. This is mostly related to the need to be guided through diagnosis, to validate therapeutic management, to discuss the goals of care, or to know more about a disease.
5. **International Collaboration:** The GRRR-OH has a strong collaboration with colleagues outside France. The GRRR-OH is originally French and Belgian. Also, since 2015, the multinational network named Nine-I has broadened the vision and expertise of the GRRR-OH. Experts from 16 countries (68 ICUs) have played an active role and have opened discussions, raised controversies, and brought new area of expertise to our group. In the future, we will be seeking to develop collaborations with everyone at stake and interested with the management of immunocompromised patients. We look forward to collaborating with our colleagues and friends from the Middle-East, Asia, Australia, and New-Zealand, and from everywhere in the world.

Conclusion

In immunocompromised patients admitted to the ICU, there are significant discrepancies in survival rates across centres. Research should help understand what the main determinants of this centre effect are, and how these differences could be addressed at the bedside. Moreover, teaching opportunities are an efficient way to transfer knowledge from experienced to less-experienced centres. The GRRR-OH and the Nine-I are research groups that provide several opportunities to share information, improve clinician skills, and transfer knowledge to ICU specialists about the care of immunocompromised patients. ■

Key points

- Educating ICU clinicians to improve their clinical skills when managing immunocompromised patients remains a major endeavour.
- The Groupe de Recherche en Réanimation Respiratoire chez les patients d'OncoHématologie (GRRR-OH) is a group of 32 centres in France and Belgium performing studies about acute respiratory failure in immunocompromised patients.
- Nine-I is a research network that focuses more broadly on all immunocompromised patients, with special emphasis on cancer patients.
- The Blood Diseases in the ICU is a training course that covers malignant and non-malignant haematological diseases.

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Challenges in the Management of the Critically Ill Patient

Interview with Massimo Antonelli, Prof. of Intensive Care and Anesthesiology, Università Cattolica del Sacro Cuore, Rome Italy

Massimo Antonelli is a Professor of Intensive Care and Anesthesiology at the Università Cattolica del Sacro Cuore, Rome, Italy. He serves as the Director of the Dept. of Anesthesiology and Intensive Care and Emergency Medicine and of the General ICU, Postoperative ICU and Neurosurgical ICU of the Fondazione Policlinico Universitario A. Gemelli IRCCS. He is also the Director of the School of Specialty in Anesthesiology and Intensive Care Medicine. Prof. Antonelli's scientific fields of interest and research include noninvasive ventilation, mechanical ventilation, ARDS, shock, sepsis, and infections. He has been involved as a principal investigator in many Phase II-III clinical and international trials in ICU patients. Prof. Antonelli is the author of more than 300 papers. The majority of these scientific publications are on several aspects of noninvasive ventilation, ARDS, shock, and sepsis. He has been invited as a lecturer or chairman in more than 300 international meetings. Prof. Antonelli spoke to ICU Management & Practice about the major challenges in the management of the critically ill patient.

Sepsis remains a major health problem in the ICU and is associated with high mortality rates. What do you see as the main challenges when managing sepsis and septic shock?

The first real problem in regards not only to septic shock and sepsis, but also to ARDS, is that we, as intensivists, treat the syndromes and not really the diseases. Sepsis is induced by an infectious disease condition, and septic shock is the most severe expression of the sepsis. The kind of germs that can induce the infection may be quite diverse. Some of them can be multidrug-resistant. In addition to that, it depends if we are speaking about treating the sepsis that has been developed in the community or within the hospital.

The main challenge with the recognition of sepsis is also the timing. We never know when the real first moment of sepsis started, and consequently, the recommendation is to try as much as we can to have an early recognition of symptoms to start early therapies. There is a lot of discussion concerning if it is better to concentrate on the main therapeutic interventions, within one hour or three hours etc. But whatever the personal attitude, nonetheless, the main issue is timing. The earlier it is, the better it is.

The Surviving Sepsis Campaign is geared towards reducing mortality from sepsis. What are the main priorities of this campaign?

The main priority of the Surviving Sepsis Campaign is to have a worldwide common protocol, and a common approach to sepsis. Together with the American Society of Critical Care Medicine (SCCM), the founder of the Surviving Sepsis Campaign (SSC) with the European Society of Intensive care Medicine (ESICM), we recently involved the WHO in the campaign. The WHO launched an international action involving countries of all the continents in

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order to increase the awareness concerning the sepsis concept and its risks. The priority is not only speaking to the doctors and the personnel working in the hospital in order to identify the syndrome in the earlier phases and starting an appropriate therapy soon, but also giving recommendations to the general population in various contexts with the intent of preventing sepsis and the evolution of the infection towards the most dangerous complications.

I would also say that the main priority here is sharing a common mentality and trust for all the physicians working in any place of the world. But at the same time, educating the community and not only the Academy, on which could be the best priorities in sepsis, what sepsis means and how we can treat and recognise it. This is also one of the essential priorities of the Surviving Sepsis Campaign together with research for future development.

The Berlin Definition of ARDS still remains controversial. Why do you think that is? And how do you think early recognition of ARDS can be improved? Which interventions are crucial for improving the outcomes of ARDS?

Both ARDS and septic shock are syndromes. And in the case of ARDS, it can be multifactorial and have different causes. I give you some examples. A patient with severe trauma may develop ARDS. A patient with sepsis which is outside the lung - as an intrabdominal sepsis - may develop ARDS. A patient who has an intoxication may have ARDS. During a burn, the smoke that the patient inhales may induce ARDS. It means that the causes can be vastly different and our possibilities to treat the patient in the best way is to put together the various interventions and grade them depending upon the severity and chronology. What we did, when we coined the Berlin Definition of ARDS, was to make an effort to allocate the possible interventions in the moments of ARDS. We identified three different classes – mild, moderate and severe. For each of these classes, there was the recommendation of using early interventions focused in specific moments. In other words, if we have a severe ARDS that starts with the most dangerous situation, it would be better to apply protective ventilation, pronation and/or ECMO, while in the very early phases of ARDS, you may attempt to ventilate the patient non-invasively, keeping the spontaneous breathing alive. The other point is that with the ARDS definition, it was impossible to identify a marker that could provide an early diagnosis and prognostication. Due to this reason our approach to ARDS remains difficult. How can we improve the outcomes? The research will continue, but for the moment, a correct protective mechanical ventilation is crucial.

> "the main priority is sharing a common mentality and trust for all the physicians working in any place of the world"

Weaning from mechanical ventilation is a challenge in ICUs. Delays in weaning can cause complications. Do you think there are any protocols that could be implemented to ensure patients can be weaned off as quickly as possible?

Indeed, it is something that already exists. There are various attitudes and behaviours depending upon which side of the Atlantic Ocean you are. In the United States, for instance, they extensively use the protocols for weaning the patients, and they are carefully and strictly respected by the nurses. But the structure of the ICU in the United States is substantially different because the doctors are not obliged to stay within the unit all day long, and also during the night. In Europe, we also have very similar protocols in order to speed up the weaning from mechanical ventilation as much as we can, but we have the advantage of having doctors 24 hours a day, seven days a week within the unit. This allows you to check your patients not only at specific moments, but many times a day. And this helps in reducing the amount of sedation when needed, and this can also be a helpful tool for decreasing the period of mechanical ventilation.

We have a number of studies that have been published on the various ways to wean patients from mechanical ventilation. I would say that in some studies, one methodology prevails, but in others the results might be exactly the opposite. This means that the best protocol does not exist. The point is that the weanability of a patient should be systematically and repeatedly checked. You can wean with pressure support or the T-piece trial or by using a trial of non-invasive ventilation after the extubation. All these possibilities can be effective. In large part, these choices depend on the physician's preferences. We have the protocols, we know the principles, but then we have to think intelligently as to how to apply those principles and protocols to that given patient.

Another major issue facing healthcare is the growing prevalence of antibiotic resistance. In your opinion, what are the key reasons for this antibiotic crisis?

This is a very complex situation. I think that the extensive use of antibiotics in agriculture was the main cause of this diffusion. Together with that, there is also the large use of antibiotics on the part of the general practitioner that has increased over the last 20 years, certainly after the Second World War. The overuse

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of these antibiotics for conditions that do not necessarily need a prescription of antibiotics selected those germs that are more dangerous. Together with that, other factors such as genetic predisposition, geographical reasons, level of staffing and infection management may favour the dissemination of germs. Data from the European Infectious Disease Control Agency show that most of the multidrug-resistant germs are concentrated in Southern Europe, in South America, and in the Far East.

It might be easier to control and reduce the risk of transmitting infection when you have a one-to-one nurse-patient ratio. Because of budget constraints and other problems in staffing, sometimes the ratio can increase to one nurse for two or three patients. In such situations, it may become more difficult to respect the best rules for preventing infection cross-transmission.

How do you think the misuse or overuse of antibiotics can be controlled keeping in mind the fact that any delay in the use of antibiotic treatment in critically ill patients can increase the risk of mortality?

This is very important. I think that in my hospital, as in many other hospitals nowadays, we apply stringent policies for antibiotic stewardship, which means not only paying attention to a careful prescription of an antibiotic, but also being ready to deescalate. For instance, when starting with a broad spectrum empirical antibiotic therapy for a serious infection, and getting the results from the microbiological laboratory, you may realise that the germs that you had supposed to be the cause is more susceptible to antibiotics with narrower spectrum. In this case, the broad-spectrum antibiotic should be deescalated to a narrow-spectrum antibiotic. At the same time, when we talk about the antibiotic stewardship, it also means speaking about antibiotic policy such as which procedure to use before surgery, the adequate selection of antibiotic, and limiting prescription of the most recent generation antibiotic to those patients where these molecules cannot be replaced by more common ones. Thus, when we speak about stewardship. it is not only a matter of one single possible intervention, but a general broad policy to approach the entire problem in the hospital.

Two other major issues are sedation and pain management in critically ill patients. What strategies can be used to maintain the minimum possible level of sedation in critically ill patients? Do you think any one particular sedative drug is better than others?

I think that the patient should be sedated as little as possible in the ICU, but obviously, we shouldn't make any confusion between sedation and analgesia. Patients shouldn't have any pain for their conditions, but that does not mean they always need to be sedated. This can be true during the most serious moment of their disease, but after that, as soon as the doctors check the possibility of weaning from mechanical ventilation, the sedation reduction or suspension become mandatory. Never oversedate, and when using drugs, it is always better to titrate and individualise on the specific needs of the patient. Together with that, pain management is the essence. It Italy, we have a specific law that imposes checking for the presence of pain several times a day in all the patients and reporting interventions and outcome. I think that the nurses and doctors should give great attention to this specific aspect.

What about delirium? Do you think that's only connected to sedation or do you think there are other factors at play and how do you think the risk can be reduced?

Delirium is multifactorial. The ICU environment may "per se" induce delirium. In the ICU, throughout night and day, there is always noise because the noise is invariably present due to the alarms and continuous activities. We should try to respect the night time and hours. We should dim the lights, and reduce the noise as much as we can. However, we should pay attention on ensuring prevention of delirium by regularly checking for it. One of the mistakes commonly committed is to pretend that certain drugs that are used for sedation could prevent delirium. This can be wrong. One example is dexmedetomidine, which is a fantastic sedative for collaborative sedation, but we cannot pretend that once the delirium occurs, this drug can be curative as it is not conceived as an anti-delirium agent.

You've also indicated that you have an interest in humanising patient care in the ICU. What measures do you think can help achieve this?

First of all, it depends on staffing and many other organisational factors. Allowing the relatives to stay within the unit and within the rooms of the loved ones as much as possible is very beneficial in helping the humanisation of care.

I always tell my residents and students that when you have a patient in front of you, you should think that this is not just a patient but also a person and then ask yourself how you would like to be treated if you were in the shoes of that person. Always try to have the best human touch, respect the dignity and speak to them and involve the patients and/or the relatives in the therapy plan, not forgetting their religious beliefs. ■

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AGENDA

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

OCTOBER

10-12 8th Annual Johns Hopkins Critical Care Rehabilitation Conference
Baltimore, USA
https://iii.hm/yc1

12-16 EUSEM 2019: 13th European Emergency Medicine Congress
Prague, Czech Republic
https://iii.hm/yc2

14-18 World Congress of Intensive Care 2019
Melbourne, Australia
https://iii.hm/yc4

15-16 ESA Focus Meeting on Perioperative Medicine 2019: Mother and child
Rome, Italy
https://iii.hm/yc5

19-23 ANESTHESIOLOGY® 2019
Orlando, USA
https://iii.hm/yc6

28-31 Qatar Critical Care Conference 2019
Doha, Qatar
https://iii.hm/yc7

NOVEMBER

9-10 7th European Conference on Weaning and Rehabilitation
Amsterdam, Netherlands
https://iii.hm/yc8

10-13 Critical Care Canada Forum 2019
Toronto, Canada
https://iii.hm/yc9

13-16 WAMM 2019 - World Airway Management Meeting
Amsterdam, Netherlands
https://iii.hm/yca

19-21 13th Pan Arab Critical Care Congress
Cairo, Egypt
https://iii.hm/ycb

19-21 Echocardiography for Hemodynamic Monitoring 2019
Brussels, Belgium
https://iii.hm/ycc

DECEMBER

3-5 25th Postgraduate Refresher Course on Intensive Care and Emergency Medicine
Brussels, Belgium
https://iii.hm/ycd

4-6 DIVI 2019 - German Interdisciplinary Association for Intensive Care and Emergency Medicine Congress
Hamburg, Germany
https://iii.hm/yce

9-11 ICS State of the Art 2019
Birmingham, UK
https://iii.hm/ycf

11-14 ESEM 2019 - Emirates Society of Emergency Medicine Conference
Abu Dhabi, UAE
https://iii.hm/ycg

15-18 Update on Long-Term Outcomes
Rome, Italy
https://iii.hm/ych

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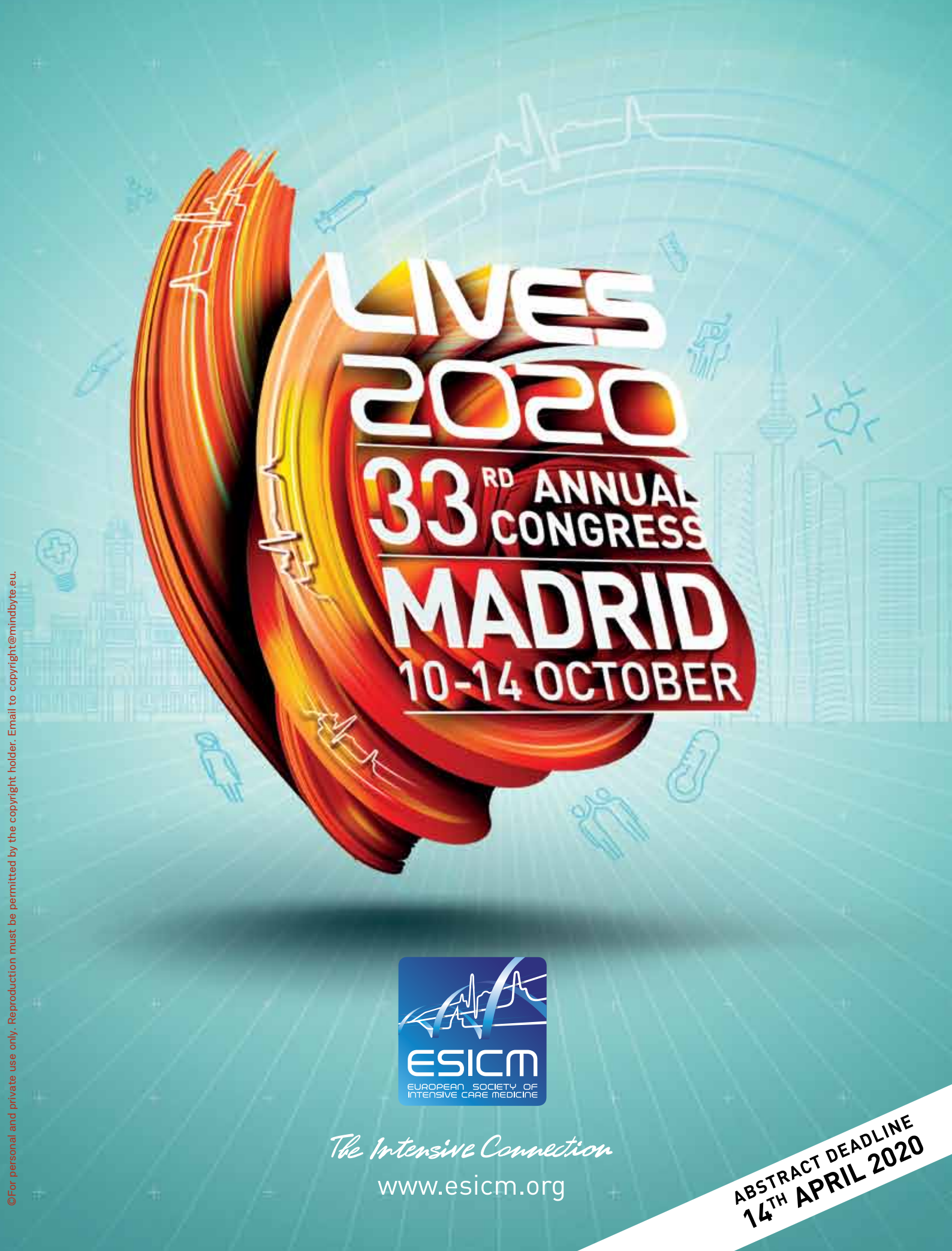

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By your side from behind the scenes

Aspen is committed to help anaesthesiologists and intensivists through major collaboration with medical societies. Although you won't see Aspen booth at ESICM lives 2019, we care about you and the future of intensive care.

We look forward to seeing you. In the meantime, feel free to watch these two clinical sessions:

Sedation practices in the ICU

Chairmen: **Prof. Michael Sander** *(Germany)*
& **Prof. Jean-Daniel Chiche** *(France)*

Safety first: insights from clinical pharmacists.
Dr. Robert Shulman *(United Kingdom)*

What a difference a drug makes?
Prof. Jean-Daniel Chiche *(France)*

Good past - better future?
Prof. Marc Léone *(France)*

Pain management in the ICU

Moderator: **Prof. Jean-Louis Vincent** *(Belgium)*

How to manage sedation analgesia for a patient centered care in ICU?
Prof. Gerald Chanques *(France)*

Opiate sparing analgo-sedation in ICU. The impact of regional anesthesia.
Prof. Xavier Capdevila *(France)*

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