ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

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Nilesh M. Mehta
Associate Professor of Anesthesia
Harvard Medical School

Director of Quality & Outcomes
Critical Care Medicine
Director, Critical Care Nutrition
Boston Children's Hospital
Boston, USA

Immediate Past President
American Society for Parenteral
& Enteral Nutrition (ASPEN)
USA

nilesh.mehta@childrens.harvard.edu

@NileshMehtaMD

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

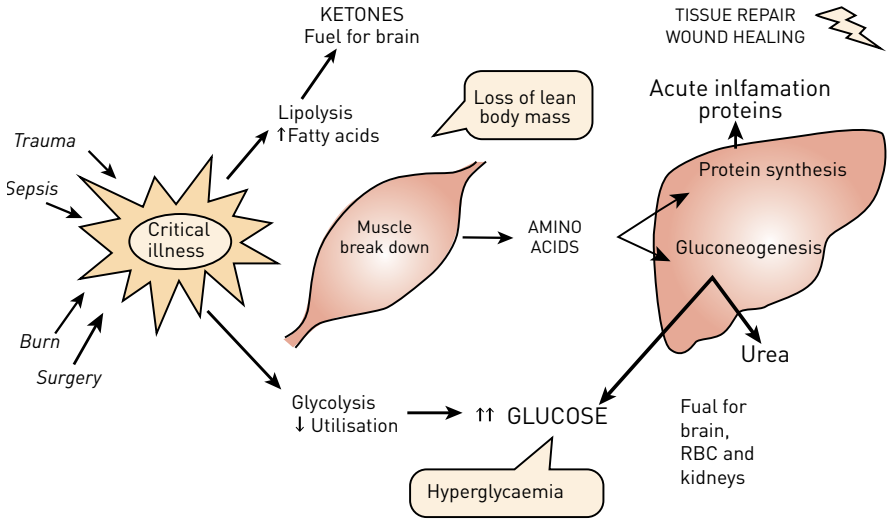

Figure 1. The stress response to critical illness – protein breakdown. Source: Mehta and Jaksic 2008.

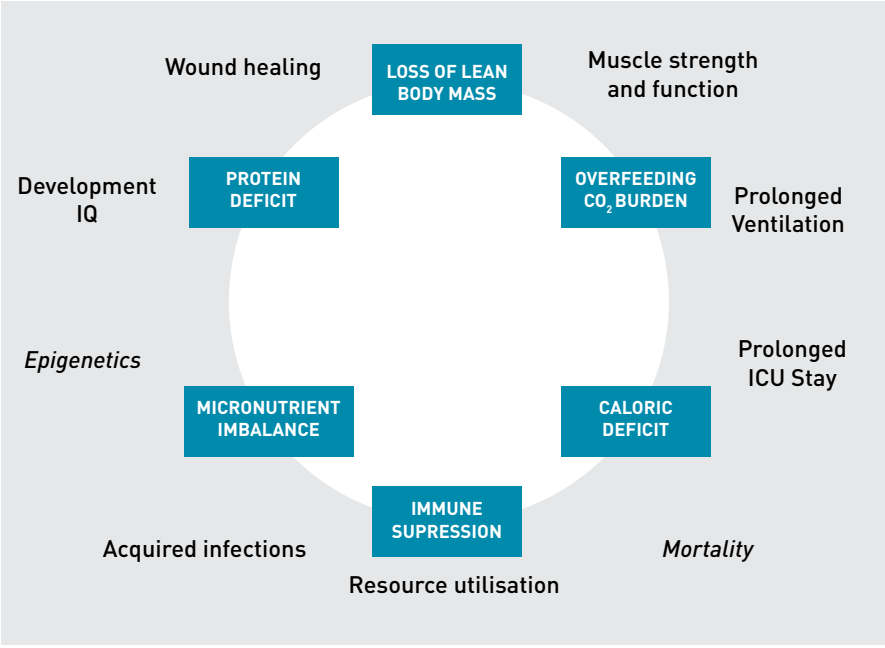

Figure 2. Outcomes for critical care nutrition trials – call for uniform data elements

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

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	

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.

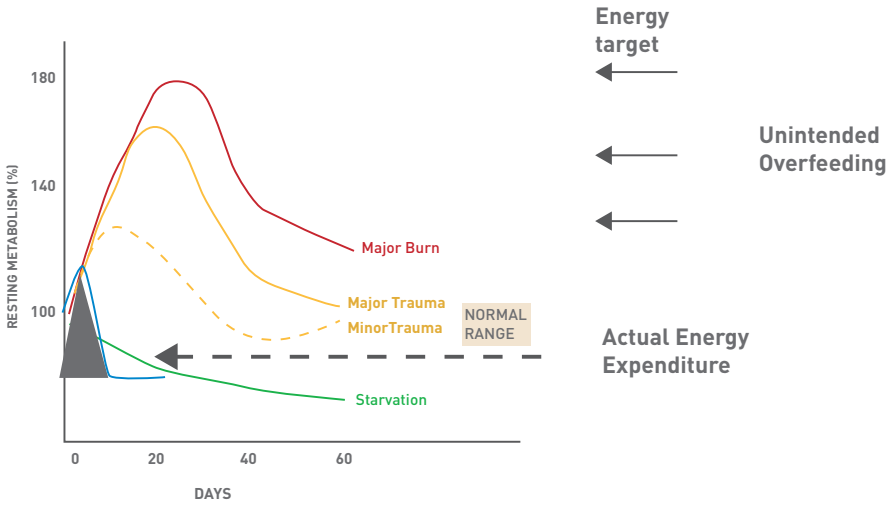

Figure 3. Energy targets and the potential for overfeeding during critical illness

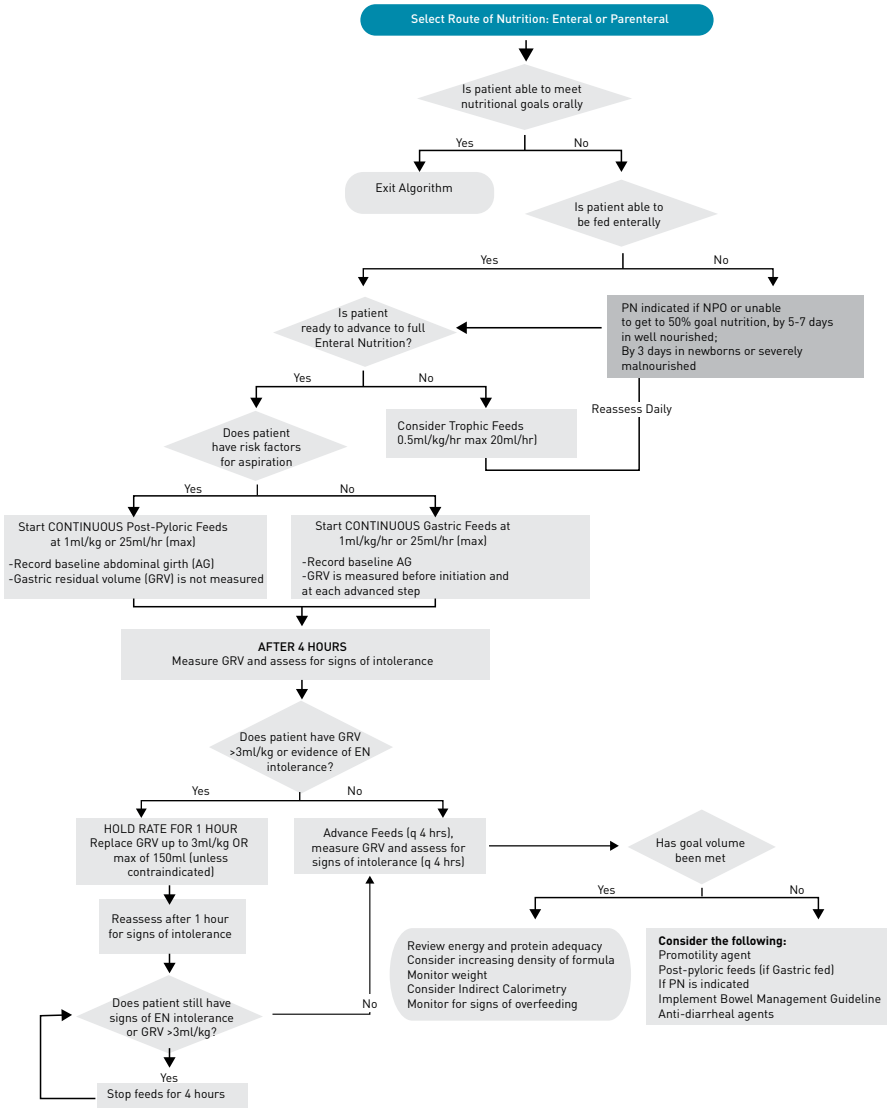

Figure 4. Stepwise EN algorithm. Source: Hamilton et al. 2014.

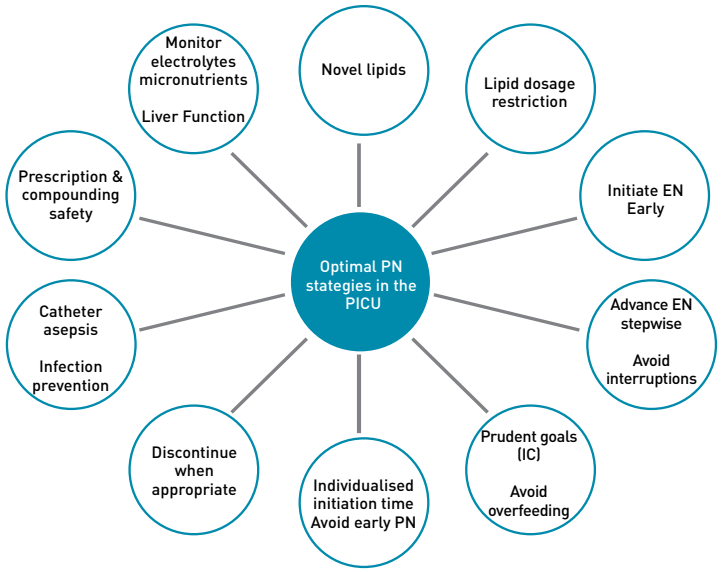

Figure 5. Strategies for safe and optimal use of PN

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

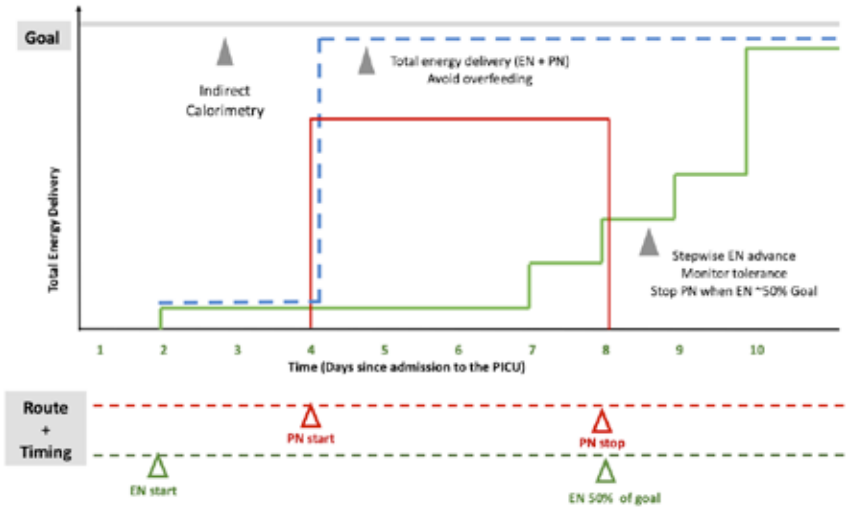

Figure 6. Stepwise EN algorithm. Source: Hamilton et al. 2014.

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?

Stephan Jakob, MD, PhD
Department of Intensive Care Medicine
University Hospital Bern
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.

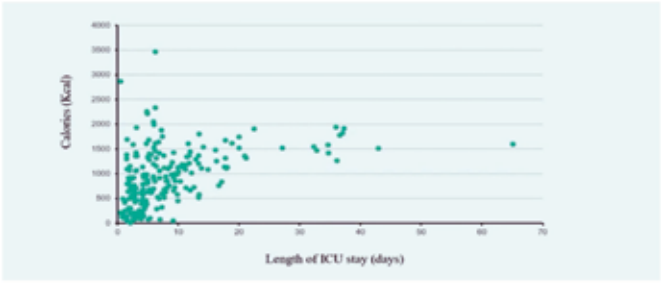

Figure 1: Daily administered nutritional calories per patient

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.

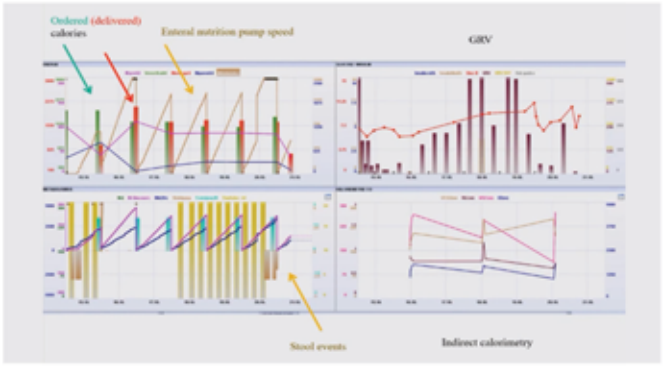

Figure 2: Nutrition delivery to the patient

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.

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

DIVINE nutritional management in ICU

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

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.

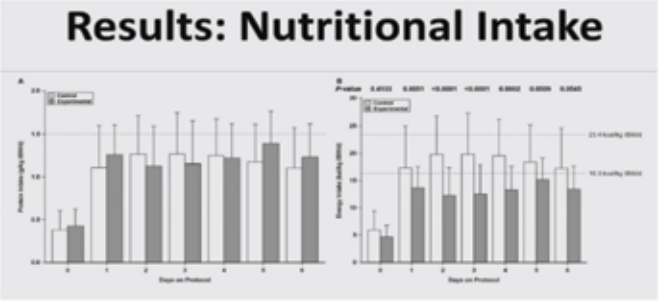

Figure 1: Results of the DIVINE study

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.

ESICM Satellite Symposium 2018

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The metabolic phenotype of skeletal muscle during early critical illness

Nicholas Hart, MD, PhD
Lane Fox Clinical Respiratory Physiology Research Centre
St. Thomas' Hospital
Guys & St. Thomas' NHS Foundation Trust
London, UK

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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