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 A study, yet unpublished, was conducted with 220 patients in our 39 bed mixed surgical medical ICU.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.

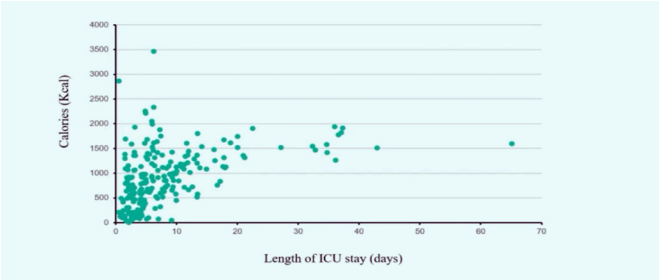

Figure 1: Daily administered nutritional calories per patient

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.

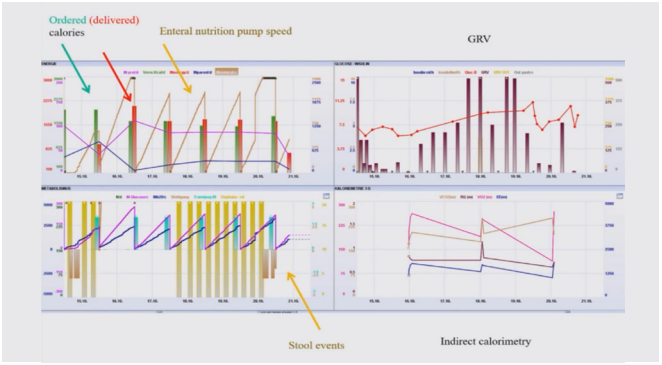

Figure 2: Nutrition delivery to the patient

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.

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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.

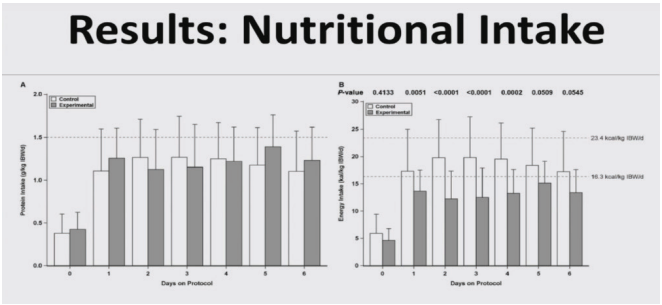

Figure 1: Results of the DIVINE study

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.

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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.

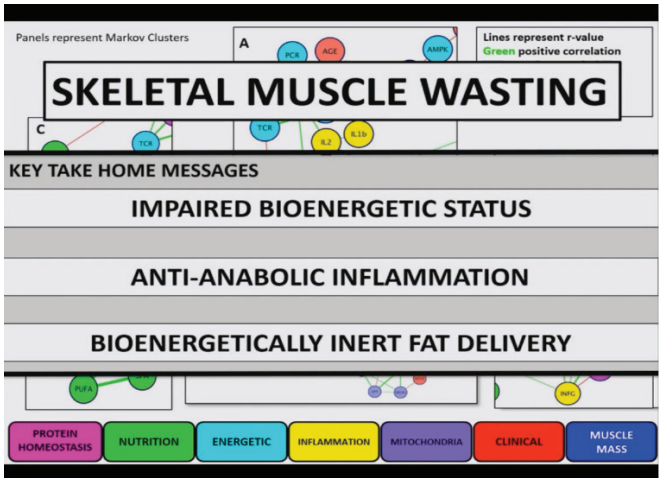

Figure 1. Skeletal Muscle Wasting

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.

References:

1. Bousie E et al. Eur. Jnl of Clin Nut. 2016; 70:1443-1450
2. van Zanten ARH et al. Clin. Nutr. 2018; 38(2):883-890.
3. Weijs et al. Critical Care 2014;18(704)
4. Zusman O et a. Crit. Care 2016;20:367
5. Doola R et al. Clin Nutr. 2019; 38(4):1707-1712
6. NICE-SUGAR Study Investigators. NEJM 2012;367:1108-1118.
7. Rice TW et al. JPEN 2018
8. Jonghe BD et al. JAMA 2002;288(22):2859-67.
9. Herridge et al. New England Journal of Medicine 2003;348:683-693
10. Puthucheary et al. JAMA 2013
11. Puthucheary et al. Thorax 2018;73:926-935