FOCUS EDITORIAL

Focus on nutrition and glucose control in the intensive care unit: recent advances and debates

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In the current article, we focus on recent articles on glycemic control, long-term metabolic sequelae of critical illness, route and amount of feeding, critical illness-associated hepatic disorders, and evaluation and impact of nutritional status of the critically ill.

Debate regarding glycemic control in critically ill patients continues. The three Leuven trial results showing improved outcome of critically ill patients with tight glycemic control (TGC) compared to standard therapy were not reproduced in other studies [1]. Importantly, the NICE-SUGAR trial demonstrated increased risk of death with TGC compared to standard care. TGC opponents suggest the Leuven results reflect high glucose delivery and the resulting provision of insulin counterbalancing the deleterious effects of glucose [1]. TGC proponents attribute benefits of the Leuven studies to the accuracy of glucose measurement tools, the variability in delivery of insulin bolus doses, the training of the nursing team, the requirement to stop intensive insulin therapy when the patients were able to eat and the need of a “gentle correction” of hypoglycemic episodes to avoid hyperglycemia rebound [2]. An intermediate strategy has been suggested with “non tight” glycemic targets with an individualized upper limit according to patient characteristics and unit logistics [3]. There is increasing evidence that pre-ICU conditions, particularly diabetes, may influence the effects of glucose control during critical illness. Chronic pre-ICU hyperglycemia (documented by HgA1c) increases the risk of hypoglycemia during the ICU stay [4]. Also, pre-admission hyperglycemia severity was associated with higher mortality risk with intra ICU

hypoglycemia. Additionally, hyperglycemia is associated with deleterious effects on the nervous system [5]. However, data from RCTs of TGC revealed mixed results. Nevertheless, prevention of hyperglycemia during critical illness is considered as a part of neuroprotective care, although the optimal blood glucose level remains uncertain [5].

What are the long-term metabolic sequelae of critical illness? In, observational data the risk of development of type 2 diabetes mellitus is significantly increased in the 3–5 years following critical illness, especially following sepsis [6]. However, it is not clear whether underlying diabetes increases the risk of critical illness or critical illness favors the development of diabetes. Further studies are required to determine the risk factors for diabetes development in critical illness survivors and who may benefit from long-term follow up.

The European Society of Intensive Care Medicine (ESICM) recently published clinical practice guidelines on early enteral nutrition (EN) in critically ill patients [7]. The guidelines suggest that early or delayed EN is preferred over parenteral nutrition (PN) and that EN be delayed in various conditions including uncontrolled shock, uncontrolled hypoxemia and acidosis. However, these guidelines may need revision in light of the CALORIES trial, which did not demonstrate harm with early PN compared to early EN in the ICU [8].

Recent randomized trials challenge recommendations regarding energy and protein targets in critically ill patients. Anorexia is increasingly considered as an adaptive response stimulating autophagy, a key mechanism in preserving immune response and muscle protection during critical illness. Restricting enteral calorie and protein intake during early phases of critical illness is associated with similar outcomes to a strategy that aims to reach full

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targets [9]. Interestingly, the concept that early supplemental PN has deleterious effect in critically ill pediatric patients was confirmed in the PEPaNIC trial, which demonstrated that late supplemental PN (initiated after day 7) compared to early PN was associated with improved outcomes. A recent meta-analysis of ICU RCTs failed to show an impact of the amount of calories or proteins on mortality, length of stay, mechanical ventilation duration, or ICU-acquired infections [10]. Hypocaloric feeding compared to standard feeding was noted to have a non-significant decrease in mortality (odds ratio, 0.8; 95% confidence interval, 0.62–1.02; $P = 0.07$).

The optimal protein supply at the acute phase of severe critical illness is also a matter of intense study. Davies et al. published a meta-analysis that did not demonstrate any impact on mortality of the amount of proteins delivered to critically ill patients. A multicenter RCT found that supplemental amino acid intake added to standard nutrition compared to standard nutrition alone did not affect the duration of renal dysfunction [11], but did increase estimated glomerular filtration rate and daily urine output. Though the data on protein and calorie delivery are intriguing, the optimal calorie and protein supply at the acute phase of severe critical illness remains unknown.

Acute hepatitis and cholestatic liver dysfunction (CLD) during critical illness are common and associated with increased mortality. A recent review of the mechanisms involved in CLD indicated that the main pathophysiological mechanism is not related to an obstacle in the bile excretion, but rather to reversal of the enterohepatic cycle with bile acid transport back into the blood, thus leading to the increase in bile blood level [12]. In addition, experimental studies suggested a protective role of bilirubin on endothelium and against oxidative stress and hyperglycemia. In humans receiving parenteral nutrition, increased bilirubin levels were associated with reduced complications. Thus, whether these alterations in hepatobiliary metabolism are adaptive or reflect pathological disorder is unknown, and requires further investigation.

Assessment of nutritional status in ICU patients remains limited, and existing tools (BMI, NUTRIC score and others) could not show different treatment effects with permissive underfeeding compared to standard feeding in post hoc analysis of the PermiT trial [13]. Low fat free mass as assessed by bioelectrical impedance-derived phase angle was associated with clinical outcomes in various clinical conditions including cancer, liver cirrhosis or gastrointestinal surgical patients. In a study of 931 ICU patients, phase angle was lower on day 1 in survivors than in non-survivors [14]. Similarly, critically ill patients with low skeletal muscle quality assessed by CT-derived skeletal muscle density have heightened

6-month mortality [15]. Whether monitoring of fat free mass and/or skeletal muscle quality can be used to guide nutritional support requires further studies.

In summary, the last two years have produced important insights into the nuanced nature of glucose control, hypocaloric feeding and muscle measurements. Stimulating perspectives requiring further investigations include personalized glycemic control, deliberate low protein and low caloric supply at the acute phase of critical illness and monitoring of muscle mass and quality during and following an ICU course.

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References

1. Marik PE (2016) Tight glycemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med* 42:1475–1477
2. Gunst J, Van den Berghe G (2016) Blood glucose control in the ICU: don't throw out the baby with the bathwater! *Intensive Care Med* 42:1478–1481
3. Preiser JC, Straaten HM (2016) Glycemic control: please agree to disagree. *Intensive Care Med* 42:1482–1484
4. Egi M, Krinsley JS, Maurer P, Amin DN, Kanazawa T, Ghandi S, Morita K, Bailey M, Bellomo R (2016) Pre-morbid glycemic control modifies the interaction between acute hypoglycemia and mortality. *Intensive Care Med* 42:562–571
5. Sonnevile R, Vanhorebeek I, den Hertog HM, Chretien F, Annane D, Sharrar T, Van den Berghe G (2015) Critical illness-induced dysglycemia and the brain. *Intensive Care Med* 41:192–202
6. Hsu CW, Lin CS, Chen SJ, Lin SH, Lin CL, Kao CH (2016) Risk of type 2 diabetes mellitus in patients with acute critical illness: a population-based cohort study. *Intensive Care Med* 42:38–45
7. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, Fruhwald S, Hiesmayr M, Ichai C, Jakob SM, Loutet CI, Malbrain ML, Montejo Gonzalez JC, Paugam-Burtz C, Poeze M, Preiser JC, Singer P, van Zanten AR, De Waele J, Wendon J, Wernerman J, Whitehouse T, Wilmer A, Oudemans-van Straaten HM, Clinical EWGoG (2017) Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med* 43(3):380–398
8. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellington G, Leonard R, Mythen MG, Rowan KM (2014) Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 371:1673–1684
9. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P (2012) Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 307:795–803
10. Marik PE, Hooper MH (2016) Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 42:316–323
11. Doig GS, Simpson F, Bellomo R, Heighes PT, Sweetman EA, Cheshire D, Pollock C, Davies A, Botha J, Harrigan P, Reade MC (2015) Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. *Intensive Care Med* 41:1197–1208

12. Jenniskens M, Langouche L, Vanwijngaerden YM, Mesotten D, Van den Berghe G (2016) Cholestatic liver (dys)function during sepsis and other critical illnesses. *Intensive Care Med* 42:16–27
13. Arabi YM, Aldawood AS, Al-Dorzi HM, Tamim HM, Haddad SH, Jones G, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Mundekkadan S, Kumar A, Bagshaw SM, Mehta S, Ttg Permi (2017) Permissive underfeeding or standard enteral feeding in high- and low-nutritional-risk critically ill adults. post hoc analysis of the permit trial. *Am J Respir Crit Care Med* 195:652–662
14. Thibault R, Makhlouf AM, Mulliez A, Cristina Gonzalez M, Kekstas G, Kozjek NR, Preiser JC, Rozalen IC, Dadet S, Krznaric Z, Kupczyk K, Tamion F, Cano N, Pichard C, Phase Angle Project I (2016) Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study Phase Angle Project. *Intensive Care Med* 42:1445–1453
15. Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Twisk JW, Oudemans-van Straaten HM, Weijs PJ (2016) Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. *Crit Care* 20:386