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## **A broader perspective of nutritional therapy for the critically**

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In this edition of Current Opinion in Clinical Nutrition and Metabolic Care, the focus is on areas that are clinically relevant and for which there has been recent data to inform understanding. The objective of this edition provides the reader with a broader perspective of nutritional therapy for the critically ill (Figure 1).

With data available from several large trials comparing energy delivery [1-4] and the recent release of the TIACOS International trial [5], it is timely to evaluate whether an energy deficit during critical illness affects outcomes [6]. Frankenfield and Pearson use the character Wilkins Micawber from David Copperfield, who opined that it was expenditure, rather than income or input, which determines happiness (ref this paper). So, does the Micawber principle apply to energy expenditure in the critically ill? Notwithstanding the variable precision between different methodologies to quantify energy expenditure [7], the take home message from this systematic review is that, at least for now, accurate measurement of energy expenditure with indirect calorimetry does not need to be implemented for every critically ill patient. However, the authors do observe signals of benefit when attempting to measure energy expenditure and advocate for ongoing research using indirect calorimetry.

Dong and Karvellas summarise the use of technology to optimise nutritional therapy in the critically ill (ref this paper). Given the substantial challenges of identifying which critically ill patients are most likely to benefit from nutritional therapies [8], the authors reviewed the existing methodologies available to quantify muscle mass during critical illness. The authors suggest that the use of bedside techniques, such as ultrasound to quantify muscle mass, may facilitate individualization of nutritional therapy and thereby improved outcomes [9-11]. However, once technology has identified those at

greater nutritional-risk, the question remains: Do these patients benefit from early enhanced feeding or, conversely, from a more restrictive approach? Accordingly, robust evidence of a patient centred benefit is required before such technologies receive recommendation for widespread clinical use.

Recent trials of pharmacology administration of micronutrients have not established superiority of treatment with an individual vitamin [12-16]. Berger and Manzanares review the literature related to selenium, vitamin C, thiamine and vitamin D (ref this paper). The authors argue that administration of a single micronutrient has less likelihood of being effective than exogenous administration of moderate doses of multiple micronutrients and that deficiency needs to be quantified relative to inflammation – with future studies categorising patients as having sepsis or no sepsis – and to only administer the intervention to those with substantial deficiency. Regardless of whether the future is with administration of single micronutrient at pharmacological doses or combination micronutrients to achieve physiological dosing, there is an urgent need for parallel study to develop rapid and reliable point of care testing of various micronutrients so that patients with deficiency can be identified [17]. Whether such testing should rely on direct assessment of serum/tissue concentrations or indirect markers of micronutrient-dependent metabolic homeostasis (*such as serum homocysteine to methionine ratios*) remains to be established.

Many of the large nutritional trials recently completed only enrolled patients from developed countries. The location of the trial may be an issue as the prevalence of overweight or obesity increases in critically ill patients admitted to intensive care units (ICUs) in developed countries. In addition to different staffing models, availability of

drugs and technology, the proportion of overweight patients may affect the response to nutritional therapy – e.g. the mean (SD) body mass index for participants in EDEN (full: 30.4 (8.2) and trophic 29.9 (7.8) kg/m<sup>2</sup>), EPaNIC (late PN 26.2(4.7) and early PN 26.5(5.1)kg/m<sup>2</sup>), PermiT (standard 29.7 (8.8) and permissive 29.0 (8.2) kg/m<sup>2</sup>) and TARGET (1.0 kcal/ml 29.3 (7.9) and 1.5 kcal/ml 29.2 (7.7) kg/m<sup>2</sup>) [1-4]. Dixit and colleagues have written a thoughtful piece helping readers to understand the external validity of recently conducted nutritional trials to patients from developing countries and offer suggestions for the future (ref this paper). It is clearly a priority for all clinicians and researchers to support efforts to ensure trials include a proportion of patients from developing countries and that leadership from these countries ensure evidence is valid and trials address questions relevant to patients from their region.

Studies in health and ambulant populations have identified that intermitted fasting may improve outcomes [18]. Bolus feeding, on the other hand, may hold promises in overcoming anabolic resistance [19]. Given the plausible beneficial effects for the patient in the ICU, Puthuchery and Gunst provide a timely review related to intermittent feeding and/or fasting during critical illness (ref this paper). While recent trials provide important preliminary information about the use of intermittent feeding / fasting in the critically ill [20, 21], gastroparesis during critical illness is a potential confounder [22]. Markedly delayed gastric emptying will affect the duration of feeding interruption needed to induce a fasting response and may mean that bolus feeding needs to be delivered directly into the small intestine to stimulate the required response.

Reintam Blaser and van Zanten provide the reader with a thorough review of electrolyte disturbances during the initiation of nutritional therapy and a pragmatic approach to reducing the prevalence of refeeding syndrome in the critically ill (ref this paper). The authors highlight that while a rapid reduction in plasma phosphate when introducing nutrition is a suitable approach to diagnose refeeding syndrome, the nadir concentrations that are currently used are based on the distribution of plasma phosphate recorded in samples obtained in health – and these may not reflect thresholds of clinical effect in the critically ill [23]. Given the interest surrounding the NUTRIREA-2 trial and a recent pilot trial comparing trophic feeding to no enteral nutrition [24, 25], Shukla and colleagues reviewed the evidence for and against the introduction of enteral nutrition when patients are requiring modest to large doses of vasopressors or inotropes (ref this paper). The authors summarise the existing evidence that enteral feeding, when commenced as ‘trophic’, ‘trickle’ or hypocaloric feeding, has plausible mechanistic benefit and clinicians should be encouraged to do this, while awaiting evidence that confirms or refutes their suggested approach.

Finally, Peterson and colleagues review the literature related to nutritional therapy during recovery from critical illness (ref this paper). There is an emerging body of evidence that energy and protein deficits after ICU discharge are just as prevalent, and possibly of greater relevance to outcomes, as they are in the ICU. The authors evaluate the barriers to adequate nutritional therapy after ICU discharge and speculate as to potential interventions that could improve patient centred outcomes.

We sincerely thank all invited authors for their outstanding contributions. We hope that the global contributions for this special edition of Current Opinion in Clinical Nutrition

and Metabolic Care will inspire clinicians and researchers to consider broader issues related to nutritional therapy.

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