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Objective Measurement of Nutrition and Metabolism in the ICU: The Future of Personalized Metabolic Therapy

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"If you can not measure it, you can not improve it."

Lord Kelvin (Paraphrased)

The wisdom of Lord Kelvin is perhaps nowhere more vital than in the modern intensive care unit (ICU) where we pride ourselves on being able to measure every facet of human physiology and its response to illness and our pharmacologic interventions to sustain and recover life. In reality, Kelvin's verbose, yet more poignant statement was actually *"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be."* Unfortunately, the reality of current ICU nutrition therapy is that we are often largely at the "*beginning of knowledge"*. Until very recently, we have been limited in our ability to objectively measure or express ICU patient's nutrition needs and metabolic responses. This has often left us, and especially, our less nutrition passionate ICU colleagues, feeling our knowledge of how best to deliver ICU nutrition care is at best "*meagre and unsatisfactory"*. To emphasize this point, *ICU physicians would never deliver vasopressors without accurate blood pressure measurements from an arterial line or blood pressure cuff; thus, I believe the ICU community has not embraced a focus on nutrition delivery being equally important to other care areas due to our current lack of ability to routinely and objectively provide nutritional and metabolic "measures" to guide care*. This must be urgently addressed if we hope to bring ICU nutrition therapy in-line with other aspects of care on ICU ward rounds. As described eloquently by the authors of the articles in this issue of *Current Opinion of Critical Care*, we are may finally be entering the early stages

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a new era where we will have an opportunity to address this crisis of providing objective measures in ICU nutrition and metabolic care.

As a primary example illustrating the new and unique opportunity we in the ICU community have to finally address the *routine and objective provision of nutritional and metabolic "measures" to guide nutrition care*, DeWaele et al (pp XX-XX - MCC270415) describe novel data for the development of a new generation metabolic cart to measure a wide range of ICU patients energy targets. It is well-known that measured energy expenditure (EE) varies greatly throughout the course of critical illness [1] and predictive EE equations have repeatedly failed to show reasonable correlation with indirect calorimetry (IC) measured values [2, 3]. Unfortunately, use of existing IC to directly measure resting energy expenditure has been challenging to implement in widespread practice as recent studies demonstrate current commercially available IC's are often inaccurate [4, 5] and the challenges of IC measurements have led to limited routine ICU IC use,[6]. To address this critical need for a next generation IC device, an ambitious undertaking was launched to finally address Kelvin's elusive directive to "*measure what you are speaking about, and express it in numbers"*. This endeavor united academic ICU leaders with industry innovation experts to address this vital deficiency in ICU nutrition therapy. This group successfully developed an accurate, user-friendly, reasonable cost, reliable metabolic cart (IC) to measure energy targets and metabolic measures in ICU/hospitalized patients. This innovative next-generation Q-NRG® IC device (Baxter, USA and COSMED Inc, Italy), has received U.S. Food and Drug Administration (FDA) approval and is now available worldwide [6]. Current data indicates this new device fills a longstanding void in ICU nutrition therapy and should finally allow for wide-spread implementation of IC in daily ICU practice, thus potentially limiting poor clinical outcomes due to the common risk of under- or overfeeding. Given this unique opportunity this new generation IC device presents [7]; it is essential we move to a culture of personalized, targeted nutrition delivery.

In order to objectively assess the metabolic and nutritional requirements of our ICU patients we must also learn to meaningfully *measure and express in numbers* our patients body composition and muscle mass. We also must be able to ultimately measure the effects of critical illness and our therapeutic interventions, including nutrition, on body composition/ muscle mass over time. Emphasizing this, routine bedside assessment of muscle mass and body composition is now recommended by new Global Leadership Initiative on Malnutrition (GLIM) consensus recommendations on nutrition evaluation[8]. The latest evidence and research imperatives for one of these new innovative techniques is described by Vallei et al from Arthur Van Zanten's research team (pp XX-XX - MCC270404) provide an outstanding overview of Bioelectric Impedance Analysis (BIA) for Body Composition Measurement and covers the range of potential clinical applications of this evolving technology in the ICUs patient. BIA is a very versatile bedside body composition device available in the ICU and is the recommended technique per GLIM criteria [8]. Recent data show correlations are repeatedly found between BIA-measured raw impedance parameters, fluid ratios, measures of overhydration, and key adverse clinical outcomes from in critically ill patients. However, BIA reference values and standardized measurement need to continue to be validated in the ICU, and interpretation of the measurements poses challenges.

Another highly promising technique to measure muscle mass at the bedside is via muscle ultrasound (U/S) as discussed in this issue by van Ruijven et al (pp XX-XX - MCC270405) from Peter Weijs's research team. The authors describe practical considerations for bedside U/S measurement of muscle mass and quality in the ICU patient. They describe most recent literature for validation and longitudinal evaluation of ICU muscle measurements over time. They conclude the use of U/S Assessment of muscle mass is clinically relevant and adds value for guiding therapeutic interventions, such as nutrition and physical therapy, aimed at maintaining muscle mass and promoting recovery in ICU patients.

In addition to the measurement of nutritional targets and body composition over time, it is imperative we continue to work to address perhaps the most challenging question we have traditionally faced in nutrition care- defining objective lab tests to "measure" malnutrition and/or catabolism over time in ICU patients. The shortcomings of albumin, prealbumin, and other existing laboratory markers of nutrition are well known. In this issue Page et al (pp XX-XX - MCC270410) from Zudin Puthucheary's research group discuss potential novel catabolism-biomarkers to attempt to characterize the extent of patient's critical illness-related catabolism and muscle mass. The authors examine a number of novel catabolism and muscle mass laboratory markers. The authors conclude of the biomarkers discussed, in Urea Creatinine Ratio (UCR) is currently most readily applicable for clinical use as it has the largest evidence base to support its role as a biomarker of persistent critical illness, but more research is needed on these and other "nutrition" biomarkers.

In addition to the urgent need to objective measure and understand of the effects of critical illness on energy needs and body composition, it is imperative we examine the effects of modern critical illness interventions on the losses and potential increased needs for specific nutrients. Recently, the widespread use of renal-replacement therapies (RRT), including continuous-RRT (CRRT), has been discovered to lead to significant losses of critical nutrients. A new and rapidly growing body of data is describing RRT can rapidly (within days) lead to significant nutrient deficiencies [9] that are known to be associated with potential significant clinical consequences and morbidities. This previously little-known and largely unrecognized clinical challenge is described in the most comprehensive scoping review of the topic published to date by Berger and a team of international subject-matter experts in this issue (pp XX-XX - MCC270411). The authors conclude, that significant losses of several micronutrients are associated with a real risk of clinically-meaningful deficiencies. These trace elements and water-soluble vitamins are known to serve essential physiologic functions, and their depletion can lead to potentially significant morbidity (such as pancytopenia and/or prolonged or permanent weakness with copper deficiency).[10] The authors further conclude that key trace elements and vitamins should be measured in prolonged RRT (ca. > 5–7 days). Finally, the authors conclude further research is urgently required in areas including of exploration of association between nutrient losses and patient-centered outcomes, and potential prospective micronutrient supplementation trials.

In addition to the adverse effects of critical illness and ICU therapies on nutritional and metabolic status, there continues to be great interest and great controversy around the role of specific nutrients in improving outcomes. Vitamin D, particularly with the new onset of the COVID-19 pandemic, continues to be among the most discussed and studied nutrient interventions. As discussed in the review by Amrein et al (pp XX-XX - MCC270409) the potential of Vitamin D as a risk predictor and the potential benefit of Vitamin D repletion appears to depend, as Lord Kelvin urges, on the accurate measurement of levels and severity of deficiency. Specific to COVID-19 risk, recent low Vitamin D levels have been associated with higher COVID-19 infection rates [11], as well as association with worse clinical trajectories. In this outstanding and comprehensive review all of the recent and ongoing Vitamin D trials in critical illness and COVID-19 are discussed in detail. The authors conclude while more large-scale randomized controlled trials of Vitamin D in critical illness and COVID-19 are needed, available data, the rarity of side effects and insignificant costs suggest that potential benefit of vitamin D supplementation in ICU and in COVID-19 appears to outweigh the risks.

In addition to specific nutrients, many patients are coming with questions around popular weight loss diets including intermittent fasting, ketotic diets, and athletes are beginning to employ ketones as an alternative fuel to promote performance. These diets and strategies all have potential applications in critical illness. We as humans are not evolved to eat continuously, or be fed continuously. Yet continuous tube feeds are utilized in the majority of ICU's worldwide. This raises key questions around potential adverse effects on circadian rhythm (often related to feeding intervals) and even more to the concept of optimal muscle anabolism. These exciting hypotheses are brilliantly covered in a review by Gunst et al and Greet Van den Berghe's research group (pp XX-XX - MCC270414). The authors describe that recent evidence shows activation of a metabolic fasting response may be beneficial to ICU recovery. Further, use of novel feeding strategies including ketone supplements, ketogenic diets and intermittent fasting regimens, may potentially serve to activate key pathways (i.e activation of ketogenesis and damage removal by autophagy) in ICU patients. Currently, there is quite limited randomized trial data studying these feeding strategies, and results to date do not show consistent benefit and further research is needed.

Finally, post-ICU recovery and survivorship must become a focus for all ICU caregivers, especially with worldwide pandemic COVID-19 has created for the ICU community. Early data in severe COVID-19 ICU survivors[12] and extensive data in other ICU patients[13] demonstrates ICU survivors experience significant post-hospital impairment in cardiorespiratory fitness (CRF), physical disabilities and prolonged recovery periods. This constellation of impairments, collectively known as post-intensive care syndrome (**PICS**) [14] burdens survivors for months to years following critical illness[13, 15] and may prove to be more severe in critically ill COVID-19 survivors[16]. Early COVID-19 studies and other ICU survivor literature strongly suggests physical rehabilitation is required to restore pre-illness function[17, 18]. Yet, no consensus on optimal measurement of deficits in CRF, targeting of dose (or exercise prescription) or a monitoring method to target such rehabilitation interventions exists, contributing to lack of benefit seen in prior ICU survivor studies[19]. A readily available solution to the challenge of objective assessment of CRF and prescription of targeted exercise in ICU survivors is use of Cardiopulmonary Exercise Testing (CPET) [20]. Whittle and San Milan address the exciting opportunity in their review, which includes some outstanding figures, in this issue (pp XX-XX - MCC270416). They show CPET has been used successfully in both athletes and in clinical applications (i.e. pre-surgical optimization) for the assessment of aerobic fitness, diagnosis of limitations in function, the assessment of risk and the prescription of pre-/post-illness rehabilitation. Specifically, CPET could be used to identify targeted heart rate goals for recovering ICU patients to optimize mitochondrial fatty acid utilization to promote recovery of mitochondrial function and promote recovery of CRF. In short, shows promise in both research and clinical contexts for targeted metabolic rehabilitation and we hope soon CPET testing will be the 'gold standard' for assessment of limitations and exercise prescription in patients recovering from critical illness.

In conclusion, as Lord Kelvin stated, we will only evolve to meaningful objective nutrition and metabolic care *when we can measure what we are speaking about, and express it in numbers. Then we will finally be able to say we know something meaningful about our practice of critical care nutrition therapy*, and we will be able to provide objective data comparable to ICU ward rounds systems (i.e cardiovascular,). *Thus*, we must utilize and refine the many newly developed opportunities and technologies *to evolve to objective nutrition and metabolic measures* during and after ICU care as the new worldwide standard of care to guide nutrition care. We will only achieve the level of science Kelvin speaks if we rapidly move to implement new objective tools and measures described in this issue. A strategy for the application of these new innovative metabolic measures and therapies that I hope Lord Kelvin would be proud of is proposed in Figure 1. It is my hope and dream that soon we will evolve to be able routinely report these objective measures on daily ICU rounds worldwide. It is only then that we will begin to ensure each ICU patient receives personalized nutrition and metabolic care delivering the right nutrition, in the right patient, at the right time to optimize clinical outcomes.

Conflict of interest:

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

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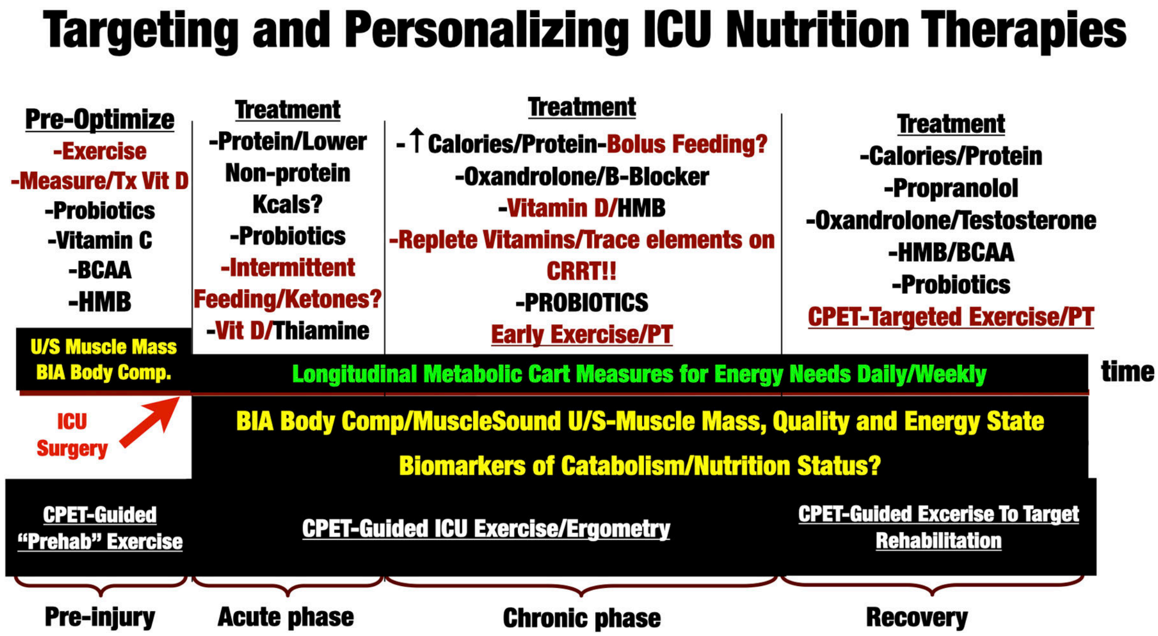

Figure 1:

Stratgey for Targeting and Personalizing ICU Nutrition Therapies. Abbreviations: U/S- Ultrasound, BIA- Bioimpedance Analysis, Body Comp.- Body Composition, CPET- Cardiopulmonary Exercise Testing, CRRT- Continuous Renal-Replacement Therapy, Vit D- Vitamin D, HMB- Hydroxymethylbutyrate, BCAA- Branch Chain Amino Acids, PT- Physical Therapy