Are we creating survivors. . .or victims in critical care? Delivering targeted nutrition to improve outcomes

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Over the last 10 years, we are proud of the fact we have finally begun to reduce in-hospital mortality following severe sepsis in some countries worldwide [1]. Further, mortality from acute lung injury has fallen dramatically, as the control group mortality in a recent large Acute Respiratory Distress Syndrome Research Network (ARDSnet) trial was strikingly only 16% [2]. But the fundamental question that must be asked is 'are we winning many battles in our ICUs, but ultimately losing the war?' Despite these improvements in ICU outcome, the same data indicating we have reduced sepsis hospital mortality by half in the last 10 years, also reveal 'we have tripled the number of patients going to rehabilitation settings' [1]. Moreover, of these new 'ICU survivors,' how many even survived a year? Troubling data from recent years reveal as much as '40–50% of the mortality within 12 months of an ICU admission occurs after the patient leaves the ICU' [3]. Commonly, patients are placed in nursing homes or rehabilitation centers, never to return home to their loved ones or return to a meaningful quality of life (QoL). Thus, leading authorities from large critical care trials groups are indicating given low ICU mortality and the high proportion of patients discharged to rehabilitation centers, that QoL, not mortality, should become the primary endpoint of future large ICU trials [1]. More practically, for all of us as ICU caregivers, we all must ask ourselves 'Are we creating survivors. . .or victims' in our ICU care.

ARE WE CREATING SURVIVORS. . .OR VICTIMS IN OUR ICU CARE? THE PATIENT PERSPECTIVE

To answer this question, perhaps we need to begin to better understand what our patients think about their QoL post-ICU? Dr. Wes Ely and collaborators at Vanderbilt University have begun to ask these key questions of patients following ICU discharge. Using patient and family interviews, his group created a website for ICU patients and their families, which we as caregivers can learn a great deal from (www.icudelerium.org). One of these interviews is with a middle-aged woman named Melissa, who previously survived a 2-year battle with leukemia. I have had the pleasure of meeting Melissa and she encouraged me to share her story with others as will be described here in brief. Melissa had been recently diagnosed with influenza pneumonia, which evolved to acute respiratory distress syndrome (ARDS) and led to an ICU stay and mechanical ventilation. Following ICU discharge, Melissa and her husband were interviewed about their experience with ARDS and recovery from critical illness. In her own words, Melissa compares her 2-year experience with leukemia and the prolonged chemotherapy she underwent with her brief experience as an ICU patient. Poignantly, she starts, 'I never dreamed after having had leukemia and done 2 years with chemo(therapy). . .I never dreamed that anything else could be worse. . .and this (her experience in the ICU and post-ICU discharge) was so much worse. It was more spiritually, emotionally, physically, intellectually challenging than even cancer. . .if you presented me ARDS and cancer, leukemia. . .I would choose the leukemia.' (See supplemental data, video #1, http://links.lww.com/COCC/A13 used with permission: Wes Ely and www.icudelerium.org). This is a statement that should shake the very foundation of those of us who have committed our lives to the care of the critically ill.

Is Melissa unique in her experience? We know from the work of Herridge *et al.* [4–6] and many others that Melissa's experience is not the

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exception, but more often the rule. Herridge *et al.* [4–6] have shown even 40 and 50-year-old ICU patients with ARDS report median Short Form-36 (SF-36) physical QoL scores of zero at 3 and 6 months post-ICU discharge. This dramatic impairment in QoL persists for 1 year, and often even more than 5 years as shown in her ongoing work. We know 50% of these relatively young ICU patients are not back at work at 1 year and one-third will never return to work following their ICU stay [4–6]. More troubling, recent data indicate that cognitive impairment will affect 50–70% [7] of our ICU patients and 60–80% [8] will be functionally impaired post-ICU. These data shed light on an epidemic that was previously unknown to most all ICU practitioners. Again, the question we must ask ourselves is, what can we do to change this and start winning the QoL battle?

WHAT IS UNDERLYING POOR PHYSICAL QUALITY OF LIFE POST-ICU?

Recent research indicates that critically ill or major surgical patients can lose as much as a kilogram of lean body mass (LBM) a day [9,10], much of it in the first week of ICU stay. The extreme of this is observed in the severely burned patient, who requires unique nutritional and metabolic support as described in this issue by Berger *et al.* (pp. 285–291). Patients may gain weight back post-ICU, but much of this weight is fat mass, not functional lean muscle mass. This is not surprising, as data from severe burn patients demonstrate that the catabolic/hypermetabolic state following injury can persist for as long as 2 years following discharge from the hospital and can markedly hinder recovery of patients lean muscle mass and QoL following injury [11,12].

CAN WE DO BETTER FOR OUR ICU PATIENTS? THE ROLE OF 'TARGETED' NUTRITION

The key question then becomes, can we change our practice and begin to create 'survivors' instead of victims? A key 'bundle' has been introduced to improve post-ICU QoL, the ABCDE bundle [13] (Fig. 1) [10]. We advocate that we should add an F and a G, with F emphasizing the basic need for targeted (F)eeding with early adequate protein and G emphasizing the role for (G)aining function and (G)rowing muscle. The ABCDE bundle has been well described by Ely and others [13], but how do we achieve the F and the G and perform the research necessary to optimize these key parts of future ICU care?

The F emphasizes that we must be thoughtful of the metabolic changes that occur following onset of critical illness and target our nutrition delivery. 'Targeted' nutrition delivery emphasizes we take into account long-standing basic metabolism data showing nutritional needs can change significantly

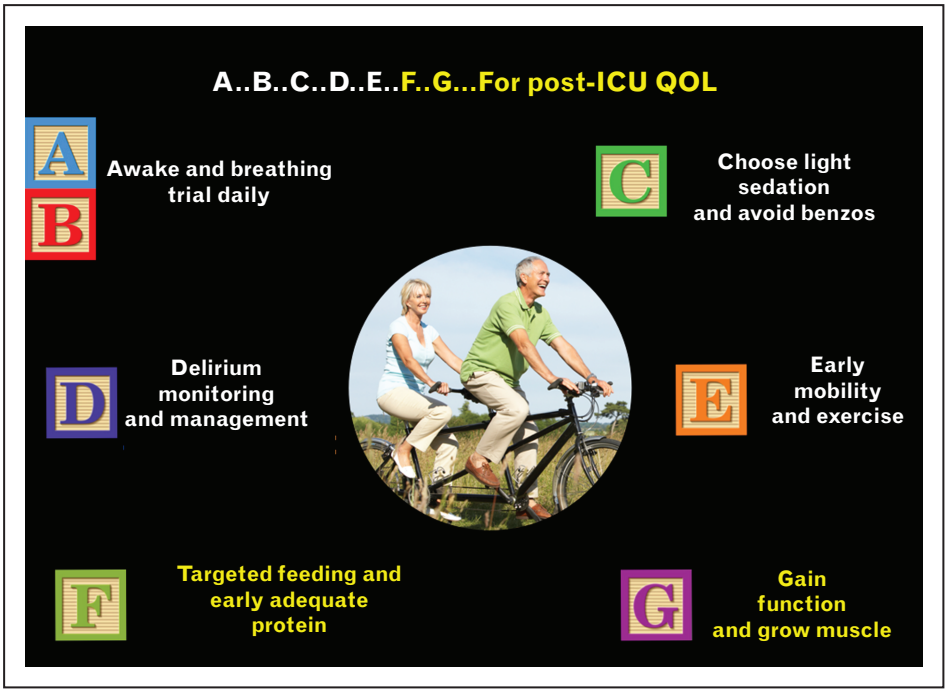

FIGURE 1. Proposed ABCDEFG bundle for improved post-ICU quality of life. Adapted from [10].

over the course of critical illness. It is well described that the early or 'acute phase' of critical illness is characterized by massive mobilization of the body's calorie reserves as muscle, glycogen, and lipid stores are broken down to drive glucose production [14,15]. This evolutionarily conserved response allows the stressed or injured human (or animal) to generate energy to escape its attacker and recover from initial injuries. This metabolic response to stress can generate 50–75% of the glucose needs during illness [15], and this glucose generation is not suppressed by feeding or intravenous glucose infusion [16]. This is described in much greater detail in this issue by Oshima *et al.* (pp. 292–298) and in other recent data by our group [16]. Further, we know that the early phases of sepsis and trauma are not hypermetabolic states, but rather the patients have a total energy expenditure (TEE)-to-resting energy expenditure (REE) ratio of 1.0 and 1.1 for sepsis and trauma, respectively [17]. Thus, caloric need does not increase in the early phases of injury (first few days postinjury). In fact, the more severe septic shock is, the lower the resting energy is, as the body 'hibernates' and shuts down metabolism in response to severe stress [18]. During the later chronic or recovery phase of critical illness, the body experiences a massive increase in metabolic needs, with TEE increasing as much as ~1.7-fold above REE [17]. These data suggest we should consider feeding less nonprotein calories early in the acute phase (first 24–96 h) of critical illness and markedly increase calorie delivery during recovery as illustrated in Fig. 2. At the same time, it is also well known that protein losses increase 4-fold in the first 24 h of critical illness [19] and we are exceedingly poor at meeting these needs [19]. Unfortunately, large, international surveys indicate

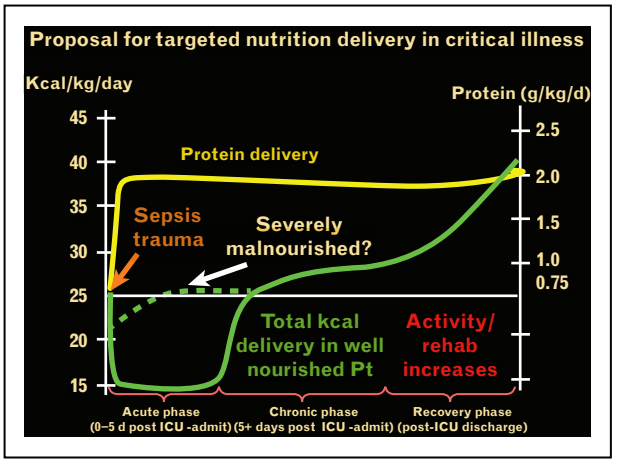

FIGURE 2. Proposal for targeted nutrition delivery across phases of critical illness.

we as ICU practitioners deliver an average of 0.6 g/kg/day of protein for the first 2 weeks following ICU admission [20]. This is one-third to half of latest ICU guideline recommended protein delivery of 1.2–2.0 g/kg/day [21]. In contrast to what is often taught, the delivery of additional nonprotein calories does not significantly improve nitrogen balance in illness beyond delivery of 50% of predicted REE [16]. Thus, an ideal 'targeted' feeding strategy is perhaps 15 kcal/kg/day of total energy during early ICU stay (acute phase), whereas ensuring patients receive optimal protein delivery (1.2–2.0 g/kg/day) as early as possible post-ICU admit (Fig. 2). The vital role of early protein administration is covered in greater detail in the review by Weijs *et al.* (pp. 299–302) in this issue. Reduced calorie delivery during the acute phase is likely not applicable in malnourished patents [i.e., patients with significant pre-ICU weight loss or Nutrition Risk in Critically ill (NUTRIC) score (without IL-6) >5] who are unlikely to have the metabolic reserve to generate needed endogenous energy [21,22]. Evaluation of nutritional status and apart from malnutrition diagnosis is further covered in this issue by Simpson and Doig (pp. 303–307). Ironically, our most recent Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) guidelines emphasize these points in updated guidelines suggesting hypocaloric parenteral nutrition (≤20 kcal/kg/day or 80% of estimated energy needs) with adequate protein (≥1.2 g protein/kg/day) be considered in patients requiring parenteral nutrition over the first week in ICU [21]. Further, in early sepsis (or acute phase of critical illness), the new SCCM/ASPEN guidelines suggest provision of trophic feeds (defined as 10–20 kcal/h up to 500 kcal/day) for initial phase of sepsis, advancing as tolerated after 24–48 h to more than 80% of target energy with early delivery of 1.2–2 g protein/kg/day [21]. Given limited higher protein, lower kilocalorie enteral feeding options commercially, total parenteral nutrition (TPN) or enteral protein supplements will be required to achieve this. TPN is a significantly more viable option now to achieve this as three recent large trials of both supplemental and full TPN support versus enteral nutrition in the ICU setting have shown that TPN use in the ICU is no longer associated with increased infection risk [23–25]. This is likely because of improvements in glucose control, central-line infection control measures, and potentially as a result of improved (nonpure soy based) lipid formulations as described in detail in this issue by Manzanares *et al.* (pp. 308–315). In support of early TPN use, the new SCCM/ASPEN guidelines indicate in any patient at high nutrition risk [Nutrition Risk Score 2002 ≥ 5 or

NUTRIC score (without IL-6 score) ≥5] or found to be severely malnourished when enteral nutrition is not feasible, 'exclusive parenteral nutrition should be initiated as soon as possible following ICU admission' [21]. A comprehensive discussion of recent evidence for the role of enteral nutrition and parenteral nutrition in critical illness is reviewed by Oshima *et al.* (pp. 292–298) in this issue. Finally, the unique issue of nutritional care in pediatric ICU patients must also be considered; this is expertly discussed by Martinez and Mehta (pp. 316–324) in their review of current knowledge in the field in this issue.

TARGETED NUTRITION IN RECOVERY PHASE? SIGNIFICANTLY INCREASED PROTEIN AND CALORIE NEEDS

As the patient enters the recovery phase, total protein and calorie delivery need to increase significantly. Data from the landmark 'Minnesota Starvation Study' performed at the end of World War II [26,27] (a study that all medical students and hospital practitioners should be taught or read themselves) demonstrate a healthy 70 kg human, following significant weight loss, requires 'an average of 5000 kcal/day for 6 months–2 years to fully regain lost muscle mass and weight' [27]. As many ICU patients suffer similar marked weight/LBM loss, we must consider that significant calorie/protein delivery will be required to restore this lost LBM and QoL. This is supported by seminal metabolism studies showing the 'average TEE in the second week of ICU stay was 47 kcal/kg/day in sepsis and 59 kcal/kg/day in trauma' [17]. This is well beyond what most deliver to recovering ICU patients; however, these are actual measured metabolic requirements of patients as they recover, and with new early ICU mobility programs this delivery of increased energy in recovery phase may be vital.

These data demand we ask, is it possible our patients have been unable to recover their QoL post-ICU for months to years because of our lack of understanding of their fundamental metabolic needs in different phases of illness? For example, the need for additional protein intake has been well described by Hofer *et al.* in a number of recent publications questioning whether it is actually 'protein deficit' and not calorie deficit that is important to improving outcome in critical illness [28–30]. The concept of adequate protein and calorie delivery improving QoL is exemplified in a recent publication from Wei *et al.* [31] in high-risk ICU patients (mechanically ventilated >8 days). Patients receiving low nutritional adequacy over the first ICU week (<50% of predicted calorie and protein need) had an increased mortality versus patients receiving high nutritional adequacy (>80% of calorie needs) after covariate adjustment [31]. These data also demonstrate that for every 25% increase in calorie/protein delivery in the first ICU week, an improvement in 3-month post-ICU physical QoL scores (as measured by the SF-36) with medical ICU patients showing significant improvements in both 3 and 6-month SF-36 scores [31]. It is vital to understand these QoL improvements are greater than the minimum clinical important differences found to be meaningful in ICU patients. A recent trial by the Australian and New Zealand Intensive Care Society group indicated that a 7.8 point change in physical QoL domain scores is considered clinically relevant in post-ICU patients [32]. The data presented from this recent publication show that for every 25% increase in caloric delivery over the first 8 days in the medical ICU, there is a 10.9 point increase in physical functioning and a 13.1 point increase in role-physical measures. Thus, these data indicate clinically significant changes in post-ICU QoL may be achieved even with just a 25% increase in calorie/protein delivery during the first 8 days of ICU stay [32].

PERSONALIZING NUTRITION FOLLOWING DISCHARGE TO OPTIMIZE RECOVERY

Finally, we must ask ourselves if patients leaving our ICUs will be able to consume adequate calories and protein to optimally recover? I think experience has taught us in most cases the answer is certainly not! Recovering patients, especially, elderly individuals, are challenged by decreased appetites, persistent nausea, and constipation from opiates, and lack of education about how to optimize their diet. To address this, a large body of data demonstrates that oral nutrition supplement (ONS) must become a fundamental in our post-ICU and hospital discharge care plan. Meta-analysis, in a range of hospitalized patients, demonstrates ONS reduces mortality, reduces hospital complications, reduces hospital readmissions, shortens length of stay, and reduces hospital costs [33–36]. A large hospital database analysis of ONS use in 724 000 patients matched with controls not receiving ONS showed a 21% reduction in hospital length of stay and for every $1 (the United States) spent on ONS, $52.63 was saved in hospital costs [37]. Finally, a very recent large randomized trial in 652 patients and 78 centers studied the effect of high-protein ONS with β-hydroxy β-methylbutyrate versus placebo ONS in older (≥65 years), malnourished (subjective global assessment class B or C) adults hospitalized for congestive heart failure, acute myocardial

infarction, pneumonia, or chronic obstructive pulmonary disease over 90 days in the hospital and posthospital period [38]. The data demonstrated that high-protein β-hydroxy β-methylbutyrate reduced 90-day mortality by ~50% relative to placebo (4.8 versus 9.7%; relative risk 0.49, 95% confidence interval, 0.27–0.90; $P = 0.018$). The number needed to treat to prevent one death was 20.3 (95% confidence interval: 10.9, 121.4) [38]. This was a key trial, as it was the first large multicenter randomized controlled trial to confirm the extensive data from smaller trials demonstrating a similar beneficial effect.

ROLE OF SPECIFIC ANABOLIC/ANTICATABOLIC AGENTS, VITAMIN D, THE GUT, AND MICROBIOME/PROBIOTICS IN RECOVERY

The data from the large ONS trial using β-hydroxy β-methylbutyrate above [32] and data discussed by Stanojcic *et al.* (pp. 325–331) in this issue emphasize that anabolic/anticatabolic interventions, such as propranolol, oxadrolone, and other agents targeted at restoring lean muscle mass (such as β-hydroxy β-methylbutyrate) may be vital in optimal recovery and survival from critical illness. As shown in Fig. 3, it is likely targeted nutrition with adequate protein delivery and 'muscle recovery-targeted' agents when combined with exercise will play a vital role in improving survival and recovery of QoL post-ICU [10]. Further, the emerging role for vitamin D to reduce mortality in vitamin D deficient ICU patients (as shown by the recent JAMA study by Amrein *et al.* [39]) is reviewed in detail by Christopher in this issue. In addition, a great deal of emphasis has been placed on the role of the gut as driver of multiple organ failure in critical illness and trauma [40]. Other key studies in this issue review the role of the gut in trauma, and evolving data on the 'gut–brain' axis by Patel *et al.* (pp. 339–346). Finally, new data expanding our understanding of the microbiome in the ICU and 'dybiosis' therapies, including probiotics and fecal microbiota transplantation are reviewed by Wischmeyer *et al.* (pp. 347–353). A summary of these interventions is described in Fig. 3.

CONCLUSION

In conclusion, we need to consider basic metabolism and historic understanding of starvation and recovery to employ targeted nutritional care to our critically ill patients. If we are to optimize patient outcomes and start creating survivors and not victims, we must focus our efforts on the ABCDEF bundles and realize our patients' nutritional needs almost assuredly change over the course of illness. Further, the presence of nutritional risk as defined by the NUTRIC score, which is now showing

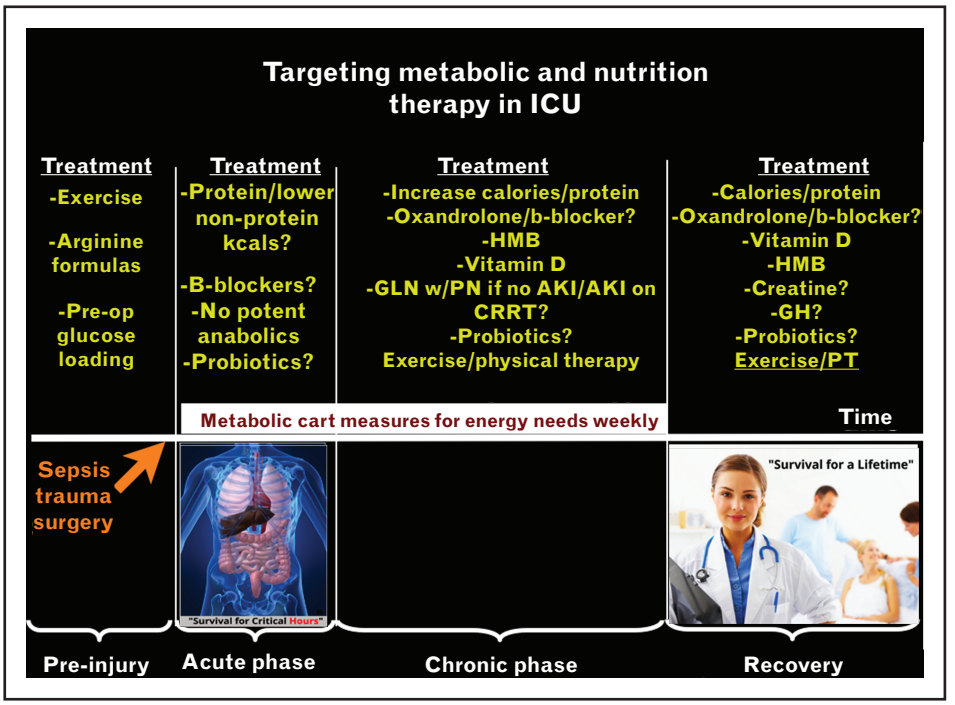

FIGURE 3. Targeted nutritional and metabolic therapy in critical illness. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; GH, growth hormone; GLN, glutamine; HMB, β-hydroxy β-methylbutyrate; PN, parenteral nutrition.

validation in other datasets, should guide how we feed our patients, with high risk (NUTRIC >5) getting aggressive early calorie and protein delivery via early enteral nutrition and/or parenteral nutrition. Lower risk patients likely need lower early calories ~15 kcal/kg/day with adequate protein (1.2–2.0 g/kg/day) as supported by the 2016 SCCM/ASPEN guidelines. Further, we must learn to target and incorporate nutritional therapies such as vitamin D, probiotics, and anabolic/anticatabolic agents to optimize our patients' chance to survive and thrive against all evolutionary odds. We have long known Mother Nature does not want our ICU patients to win this war and become 'survivors...and not victims.' If we are to begin winning this war on long-term ICU outcomes and give our patients back the lives they came to us to restore, we must ensure our patients get the right nutrition, in the right patient, at the right time!

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