# Metabolic and Nutrition Support in the Chronic Critical Illness Syndrome

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**Technological innovations in the ICU have led to artificially prolonged life, with an associated cost. Chronic critical illness (CCI) occurs in patients with prolonged mechanical ventilation and allostatic overload, and is associated with a discrete and consistent metabolic syndrome. Metabolic interventions are extrapolated from clinical critical care research, scientific theory, and years of CCI patient care experience. Intensive metabolic support (IMS) is a multi-targeted approach consisting of tight glycemic control with intensive insulin therapy, early and adequate nutrition therapy, nutritional pharmacology, management of metabolic bone disease, and meticulous attention to other endocrine/metabolic derangements. Ideally, IMS should be under the supervision of a metabolic support consultative team. Further research specifically focused on the CCI population is needed to validate this current approach.** *Key words: chronic critical illness; allostasis; malnutrition; critical care; hyperglycemia; enteral nutrition; parenteral nutrition; metabolic bone disease*. [Respir Care 2012;57(6):958–977. © 2012 Daedalus Enterprises]

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## Introduction

Critical illness in the modern ICU resolves within a relatively short period of time, results in death, or follows a protracted course of multi-organ failure, mechanical ventilation, and a need for sophisticated technological support. Advances in ICU research have focused primarily on expediting and optimizing acute critical care with cutting-edge technology, relegating those patients with prolonged critical illness to stagnant protocols and approaches.

Chronic critical illness (CCI) is a term first coined by Girard and Raffin in 1985,[1] and has become increasingly recognized as an important problem in hospital medicine. Rather than simply a temporal extension of acute critical illness, the CCI syndrome (CCIS) is a distinct and consistent clinical entity with a predictable phenotype and clinical management plan, regardless of the inciting event (eg, trauma, sepsis, or surgery). CCIS is emerging as a specific inflammatory state that is distinguished from prolonged mechanical ventilation (PMV) in patients with chronic respiratory and neurodegenerative disorders who may not have been critically ill.[2] The growing population of CCI patients carries a poor prognosis, with less than 50% liberated from the ventilator,[3] prolonged ICU and hospital stay associated with heavy financial expenditures, and 1-year mortality rates of 48–68%.[4]

The pathophysiology of CCI consists of metabolic, immune-neuroendocrine axis (INA), and nutritional derangements engendered with an initial insult but then perpetuated with unresolved critical illness, PMV, and unabated inflammation. The ultimate goal for CCI patients is liberation from the ventilator, regardless of the overall medical prognosis. This is associated not only with improved survival, but also enhanced quality of life and palliation, as well as obvious economic advantages in a healthcare system already overburdened in a frugal environment.

What has not been obvious, however, is that optimizing CCI strategies to liberate from mechanical ventilation requires meticulous attention to metabolic and nutritional parameters. As previously outlined by our group,[5–7] a metabolic approach to critical illness has been formalized. Intensive metabolic support (IMS) consists of metabolic control with intensive insulin therapy, early and consistent nutrition support, and nutritional pharmacology. CCI research is only just emerging, and therefore the rationale for these metabolic approaches is primarily theoretical and not evidence-based. In this review, the theory will be presented, followed by a review of extant evidence, most of which is extrapolated from other critical care settings. It is our hope that further clinical investigations can be designed and conducted to advance our knowledge for this very sick population of patients.

## Metabolic Model of Critical Illness

Homeostasis is the ability to maintain physiologic parameters essential for the preservation of life (eg, body temperature, pH, oxygen tension, blood pressure, and heart rate) within a narrow set-point range. As an organism is threatened by environmental or endogenous stressors, homeostasis itself is modulated by allostasis: the adjusting of homeostatic set points to achieve a new steady state, promoting "stability through change."[8] Mediators of allostasis include different products of the INA and autonomic nervous systems interacting together to determine the allostatic state of an organism at any given time. The cumulative expense of sustaining a particular allostatic state in response to a stressor, or the cost of adaptation, is termed the allostatic load.[8]

Typically, the inciting stressor in critical illness is short-lived and once absent allows homeostatic set points to return to baseline. In the setting of persistent or repetitive stressors, allostatic overload may ensue. While the adaptability of allostasis is beneficial and protective to the health of the organism in short bursts, allostatic overload can promote harmful pathophysiologic effects if not reversed.[9] In one model, type 1 allostatic overload results from energy deficit (undernutrition and starvation), while type 2 allostatic overload occurs with energy excess (overweight and obesity).[8] It is conceivable that individual variations in adaptation to stress are related to genetic mutations, polymorphisms, as well as genomic and epigenomic phenomena. Future research may some day be able to discern a patient's ability to survive critical illness based on his or her unique allostatic response.

Using the theoretical construct of allostasis, critical illness can be understood as consisting of 4 distinct stages: acute critical illness (ACI), prolonged acute critical illness (PACI), CCI, and recovery from critical illness (RCI)[6] (Fig. 1). Each of these stages has a unique pathophysiological state with metabolic targets, interventions, and end points. Another advantage of codifying these metabolic stages is to standardize clinical protocols for routine care or research.

### Acute Critical Illness

Acute critical illness is initiated following a physiologic insult to homeostasis, triggering genetically programmed allostatic mechanisms to acutely alter set points in an attempt to fully recover. These events result from natural selection, reflect the "fight or flight reaction" exhibited by our ancestors, and are considered to be "Darwinian." The mediators of allostasis are responsible for the "stress response," including hormones of the hypothalamic-pituitary-adrenal (HPA) axis (corticotropin-releasing hormone [CRH], adrenocorticotropic hormone [ACTH], and corti-

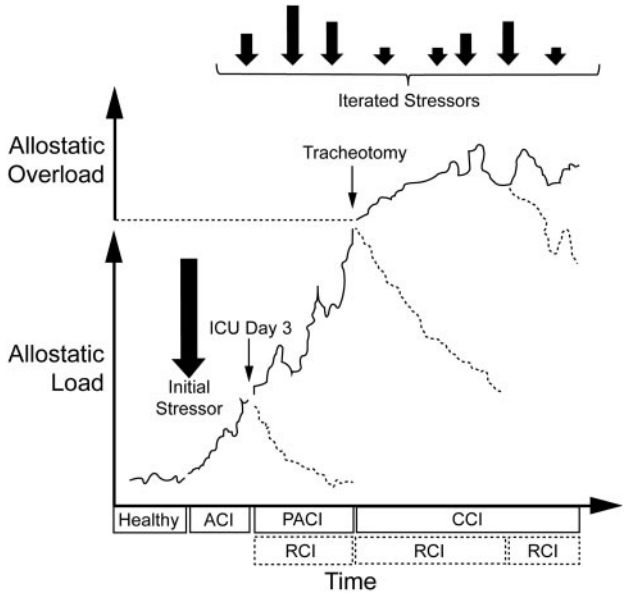


Fig. 1. Graphical depiction of effects of an initial stressor and subsequent iterated stressors on allostatic load and overload. This is a theoretical conceptualization and not based on any data. Chronic critical illness (CCI) results from repeated stressors that prevent down-regulation of the immune-neuroendocrine axis (INA). Important time points are at ICU day 3, when acute critical illness (ACI) recovers (dotted line) or evolves into prolonged acute critical illness (PACI) (solid line), and the time of tracheotomy, when PACI recovers or evolves into CCI. RCI = recovery from critical illness.

sol), catecholamines, cytokines, glucagon, growth hormone (GH), and vasopressin.[10] Organs and processes that are not immediately necessary for survival are suppressed (eg, gut perfusion, reproduction, and anabolism), while critical ones are enhanced (eg, cardiopulmonary, hemodynamics, and catabolism to mobilize metabolic fuel).

Enhanced secretion of anterior pituitary hormones is stimulated by monocyte-macrophage secretion of tumor necrosis factor-$\alpha$ (TNF-$\alpha$).[11] Acute stress-induced hypercortisolism, with a loss of the diurnal pattern of secretion following surgery, trauma, or sepsis, is associated with HPA axis activation.[12] Acute hypercortisolism contributes to shifts in metabolism from anabolic to catabolic pathways and promotes fluid retention, which confers an adaptive benefit toward hemodynamic stability.[12] Despite elevated peak and interpulse levels of GH, levels of insulin-like growth factor-1 (IGF-1) are reduced. Decreased GH receptor expression in peripheral tissues may be responsible for a state of GH resistance. The direct lipolytic and insulin-antagonizing effects of GH are promoted while the anabolic effects mediated by IGF-1 are suppressed.[13] A brief rise in thyroxine stimulating hormone (TSH) accompanies a sharp decline in triiodothyronine (T3) resulting from inhibition of 5′-monodeiodinase (causing decreased peripheral thyroxine [T4] to T3 conversion).[14] Suppression of T3, the active thyroid hormone, may exert an evolutionary advantage in the face of physiological stressors, such as starvation, by preserving metabolic expenditures and resources. Acute illness also suppresses Leydig cell production of testosterone, an anabolic hormone, with an associated transient elevation in leutinizing hormone (LH). Stress-induced elevations in prolactin also occur via hypothalamic mechanisms.[13]

The surge in counter-regulatory hormones promotes hypercatabolism, increasing availability of substrates for wound healing and cellular function. Glucose, fatty acids, and amino acids are produced for immediate use via breakdown from stores in muscle and liver. The hormonal milieu fosters a state of insulin resistance, enhancing glycogenolysis, gluconeogenesis, and lipolysis, with subsequent provision of glucose and fatty acids for substrate needs.[10] Despite the increased plasma levels of substrates, their availability to peripheral tissues is limited due to insulin resistance and inhibition of lipoprotein lipase. Levels of some substrates, such as glutamine and arginine, become insufficient due to increased demand in critical illness.[15] In contrast to the above hormone-level regulation of catabolism, direct substrate-level mechanisms can also occur. Through the effect of inflammatory cytokines and eicosanoids, pyruvate dehydrogenase, which is ordinarily suppressed with starvation, can be disinhibited; this increases carbohydrate oxidation, energy expenditure, mitochondrial dysfunction, and ultimately inefficient/futile cycling of substrates.[16,17]

Cytokines (TNF-$\alpha$, interleukin-1 [IL-1], interleukin-6 [IL-6]) and glucocorticoids reprioritize hepatic synthesis from reverse-phase reactants (eg, albumin, transferrin, and prealbumin) to acute-phase reactants (eg, C-reactive protein, immunoglobulins, and fibrinogen) in order to augment defense mechanisms and limit the spread of pathogens.[18,19] Skeletal muscle proteolysis, via cytokine stimulation of the ubiquitin-proteasome pathway, provides amino acid substrate to the liver for these processes, but at the indirect cost of lean body mass loss.[18,20] Inhibition of compensatory muscle protein synthesis may be explained by cytokine-induced reductions in anabolic hormones (IGF-1 and testosterone), and by the state of effective insulinopenia due to insulin resistance.[18]

Medical management during ACI focuses on cardiopulmonary support and correction of the inciting insult, which, if accomplished, will lead to deactivation of allostatic mechanisms and down-regulation of the INA axis. If the severity of illness is too severe to reverse, death ensues. Alternatively, if the inciting insult recurs, continues, or otherwise iterates, the patient transitions to the next metabolic stage: PACI.

### Prolonged Acute Critical Illness

In PACI, the allostatic load accrues and inflammation fails to down-regulate, even in the absence of the initial insult. Features of PACI can be recognized after approximately 3–10 days of ACI and reflect a dramatic change in neuroendocrine physiology.[21] Whereas ACI is characterized by enhanced neuroendocrine drive, PACI is distinguished by blunted hypothalamic and anterior pituitary hormone reflexes, demonstrated through combination hypothalamic-pituitary stimulation testing.[22] Hypercortisolism is maintained despite low levels of ACTH, due to direct humoral stimulation of the adrenal gland (eg, via endothelin-1).[13,22] GH and IGF-1 levels are reduced, with at least a partial reversal of GH resistance.[13] Levels of TSH, T4, and T3 are reduced, consistent with the nonthyroidal illness syndrome (NTIS), which has recently been considered a form of central hypothyroidism that may require treatment.[23] Hypogonadotropic hypogonadism is also a feature of PACI that may further enhance catabolism and poor nitrogen retention.

In contrast to the initial Darwinian metabolic changes seen in ACI and conferred by natural selection, PACI is essentially an unnatural state, devoid of evolutionary precedent, enriched by iatrogenesis, and saturated with medical technology to prolong life in those who would otherwise perish. The physiological burden of allostatic overload is no longer beneficial and produces a phenotype of persistent organ dysfunction, catabolism, insulin resistance, and, from a pragmatic and humanistic perspective, increased suffering.

### Chronic Critical Illness

The notion of a distinct metabolic CCI state was intellectually conceived in order to better define a subset of patients with prolonged critical illness manifesting a particular phenotype. This resulted from the accumulated experience of intensivists and multidisciplinary teams caring for this subpopulation of patients. By consensus, CCI commences at the time of tracheotomy, which is typically performed after 10–14 days of ventilator dependence, signifying the ICU team's subjective view that the patient will not die or be weaned from the ventilator in the near future. CCI is an allostatic overload state, whereas in PACI allostatic load accrues to become allostatic overload. The natural adaptive stress response initialized during ACI becomes maladaptive in PACI, and reaches a new steady state in CCI. Clearly, a more objective marker is needed to delineate the start of CCI and, hopefully, future research can provide this important tool. One possibility, however, may derive from a computational and systems biology context. When biological oscillators exist in a healthy person, they exhibit chaotic rhythms; these are not random fluctuations but reflect a complex system.[24,25] With illness, these rhythms become less chaotic as physiological regulatory networks lose complexity and functionality. Systems biology and network analysis may therefore provide clues to the diagnosis and management of CCI.

The CCIS explicitly describes the constellation of features typically observed in this patient population: prolonged critical care with ventilator dependence and performance of a tracheotomy; adult kwashiorkor-like malnutrition with associated protein catabolism, hypoalbuminemia, and anasarca[6]; stress-induced hyperglycemia[26,27]; bone hyper-resorption and vitamin D insufficiency/deficiency[28,29]; immune dysfunction with increased susceptibility to infection[30]; impaired neuroendocrine axes function[21]; critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) with associated profound debilitation[31]; pressure ulcers and impaired wound healing due to malnutrition, prolonged immobility, and incontinence[32,33]; neurocognitive dysfunction, including coma, delirium, and depression[34]; and excessive symptom burden.[3] These manifestations result from metabolic and INA processes described above and have previously been described in CCI or general ICU patient populations. Outcome with CCI is very poor, with prolonged ICU and hospital stays, recurrent infections and organ dysfunction, difficulty weaning from the ventilator, high morbidity and mortality, and poor quality of life.[4]

Treatment for these patients has traditionally centered on pulmonary support and ventilator weaning, though now the current paradigm is a systemic view of CCI, with an important focus on metabolic support. The goal of this newer approach is to unload the allostatic burden and to halt and then reverse the pathophysiology perpetuating the CCIS.[6] On the one hand, CCI treatment consists of meticulous attention and treatment of each metabolic derangement to optimize manifold connectedness of biological oscillators. This treatment paradigm will be discussed in detail below. On the other hand, perhaps the best CCI treatment is actually its prevention: by implementing IMS early (during ACI) to prevent transition to PACI and CCI.[7]

### Recovery From Critical Illness

The RCI stage begins with liberation from mechanical ventilation and can follow ACI, PACI, or CCI. With recovery, INA down-regulation occurs, with a gradual shift from catabolism to anabolism, reflected by an overt rise in serum albumin and prealbumin (primarily due to down-regulation of inflammation), decrease in the urinary urea nitrogen (UUN) excretion rate, and, as mentioned above, perhaps the reemergence of chaotic rhythms. Therapeutic efforts are focused on building lean mass with increased provision of nutrition, use of anabolic agents if needed,[35] correction and support of residual organ dysfunction and

metabolic deficits, rehabilitation and mobilization with physical therapy, neuropsychiatric support, and preparation for hospital discharge. In clinical interventional trials, the RCI stage represents a positive outcome.

## Nutrition Support in the CCIS

### General Remarks

Nutrition is the interaction between diet and metabolism. Malnutrition is considered when dietary intake is not commensurate with metabolic needs. This can include both over- and undernutrition. One of the prototypical features of the CCIS is the presence of inflammation and adult kwashiorkor-like malnutrition.[36] Proteolysis is increased, hepatic synthesis of albumin decreased, and cellular protein utilization increased.[18,19] As a result, hypoalbuminemia, exacerbated by dilution following large volumes of fluid resuscitation, creates a hypo-oncotic state and anasarca. Body composition is typified by loss of lean mass, anasarca, and variable fat stores. This type of malnutrition is contrasted with simple starvation or marasmic-type malnutrition, characterized by weight loss due to decreased protein-calorie intake, without substantial inflammation.[36]

Malnutrition is a common finding in the critically ill population, with reports of 43% in one study.[37,38] Protein-calorie malnutrition is associated with increased morbidity and mortality in hospitalized patients, and has been linked to negative effects on wound healing, infection rates, muscle weakness, and increased stay in the ICU population.[15,39,40]

A formal and complete nutritional assessment is generally not performed in the ICU by the medical team. There are several reasons for this: cursory assessments are typically performed by nonmedical personnel, physicians prioritize other systems, and physicians are poorly trained in nutritional medicine. Many ICU patients are already malnourished prior to admission, due to decreased dietary intake and/or gastrointestinal dysfunction. Additionally, losses of nitrogen can occur through diarrhea, vomiting, serous drainage from wounds, nasogastric tube output, fistulas, and hemodialysis.[15] Muscle wasting accelerates with immobilization, medications (eg, chronic corticosteroids), and suppressed hypothalamic-pituitary-gonadal and GH-IGF-1 axes. Furthermore, severe illness is associated with increases in resting energy expenditure (REE),[41] which raise nutritional requirements when losses are great and intake often lacking. Nutrition support is gaining recognition as a beneficial therapeutic strategy, not only to prevent losses in lean body mass, but with goals of attenuating stress-induced metabolic derangements, preventing tissue damage due to oxidative stress, and modifying the immune response.[42] If nutrition support is not initiated at the appropriate time, depending on the nutritional risk of the patient, then a critical energy debt (one that cannot be repaid) can result that negatively impacts clinical outcome.[43,44]

Providing improper amounts of nutrition is associated with poor outcomes. Studies of nutrition support in the ICU have confirmed the frequency of over- (25–58%) and underfeeding (12–35%).[45–47] Underfeeding has been linked to increased rates of total and infectious complications,[43] nosocomial bloodstream infection,[48] duration of mechanical ventilation,[49] ICU stay,[43] and mortality.[50] Impaired provision of protein increases fatigability, decreases strength and endurance, and promotes depletion of diaphragmatic muscles. This not only impedes efforts at ventilator weaning, the primary therapeutic focus in CCI, but increases respiratory muscle work and energy demands, worsening the energy debt.[2]

Overfeeding is also associated with poor outcomes, including higher rates of infectious complications, liver dysfunction, and increased mortality.[51,52] Specifically, carbohydrate overfeeding can impair glycemic control, induce hepatic steatosis, and compromise ventilator weaning due to excess $CO_2$ production. Lipid overfeeding can lead to cholestasis, hypertriglyceridemia, and potentially exacerbate inflammation through production of inflammatory eicosanoids.[6] Protein overfeeding increases oxidative deamination and surpasses the renal threshold for urea clearance, predisposing to azotemia, and with impaired hepatic urea cycling, hyperammonemia. Progressive azotemia increases obligate renal free water excretion, inducing hypernatremia and dehydration ("tube feeding syndrome").[5]

Refeeding syndrome may develop when nutrition support is started in chronically or severely malnourished patients. This condition is characterized by severe electrolyte derangements, namely hypophosphatemia, but also hypokalemia and hypomagnesemia, in addition to fluid overload and possible neurologic, cardiopulmonary, neuromuscular, and hematologic complications. Starvation, with minimal or no carbohydrate intake, reduces insulin and increases glucagon levels. In the absence of insulin, metabolic pathways shift to promote lipolysis, free fatty acid oxidation, and ketone production for energy. With the reintroduction of carbohydrates there is an increased demand for phosphorylated intermediates of glycolysis (adenosine triphosphate [ATP] and 2,3-diphosphoglycerate [2,3-DPG]), depleting phosphate stores, which are already low due to poor nutrition and usually vitamin D deficiency. A surge in insulin secretion in response to carbohydrate load shifts phosphorus, potassium, and magnesium into cells, lowering serum levels further, and has a renal antinatriuretic effect, with resultant sodium and water retention. Demand for thiamine is raised as well, predisposing to deficiency and associated complications. Other micronutrients are abnormally redistributed as well in the refeeding syndrome. Severe hypophosphatemia can impair

diaphragmatic function and impede weaning from the ventilator. For these reasons precautions must be taken when instituting nutrition support in patients at high risk for the refeeding syndrome.[53]

### Nutritional Assessment

An appropriate nutritional assessment of the CCI patient includes a thorough history and physical examination, with changes in weight or eating habits prior to hospitalization, comorbidities, functionality of the gastrointestinal tract, and the ICU course noted. A pre-hospital dry, adjusted weight is more useful than later weights following large volume resuscitation and fluid shifts, and taken on bed-scales that require adequate calibration for accuracy. The physical examination should assess for temporal wasting; sarcopenia; micronutrient deficiencies; fluid status including ascites, pleural, sacral, and pedal edema; presence of non-healing wounds or ulcers; drains and other potential losses of nitrogen.

Biochemical data provide important information on electrolyte status, which will need to be managed meticulously. Decreases in visceral proteins (eg, albumin, prealbumin, transferrin, and retinol binding protein) during critical illness are useful metabolic markers of inflammation, even though they do not directly reflect nutrition status.[19,54] Albumin levels have also been linked to clinical outcome.[55,56] Prealbumin, with a shorter half-life, has been shown to correlate with sufficiency of nutrition support and nitrogen balance, but not with outcome.[57,58]

Various instruments can be used, albeit infrequently, to assist with determination of body composition: ultrasound, dual x-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectrical impedance (BIA). Anthropometric determinations, such as the cutaneous skin-fold, are typically inaccurate due to anasarca.[43]

Several screening tools have been developed to assess nutritional risk. The Nutritional Risk Index (NRI), first described by Buzby et al[59] in surgical patients, utilizes serum albumin and percentage of usual body weight to stratify nutritional risk. The Nutritional Risk Screening (NRS 2002), developed by Kondrup et al,[60] was designed using a retrospective analysis of controlled trials on nutrition support in relation to outcome. Points are assigned reflecting the degree of undernutrition (weight loss $> 5\%$ in 3 months, reduced body mass index, decreased oral intake) and severity of disease, with nutrition support recommended for a combined score of $\geq 3$ out of 7. The NRS 2002 is a well validated tool in the general population of hospitalized patients and is widely used in Europe.[61] Other tools validated for specific patient populations include the Subjective Global Assessment (SGA) (surgical and oncology patients)[62] and the Mini Nutritional Assessment (MNA) (general geriatric population).[61] However, there is currently no available screening tool that has been validated in the CCI population. Determination of nutrition status and risk in the CCI population is therefore dependent on the clinical judgment and experience of the evaluating physician or registered dietitian. Extrapolating from other hospital scenarios, especially in the ICU, one would anticipate that nutritional risk stratification should have a substantial and beneficial impact on the metabolic care of CCI patients.

### Indirect Calorimetry Versus Predictive Equations to Titrate Nutrition Support

The gold standard for determining energy expenditure and requirements in the clinical setting is indirect calorimetry. This method calculates REE, the amount of energy required for basic metabolic processes, through the measurement of respiratory gases. Oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) reflect heat production during oxidation of substrates (substrate + $O_2 \rightarrow CO_2 + H_2O$ + heat). The modified Weir equation[41] is used to determine nutrition requirements:

$$\text{REE(kcal/d)} = ([\dot{V}_{O_2} \times 3.941] + [\dot{V}_{CO_2} \times 1.11]) \times 1{,}440$$

The respiratory quotient (RQ) is the ratio $\dot{V}_{CO_2}/\dot{V}_{O_2}$ (physiologic range 0.67–1.2) and reflects substrate oxidation (glucose RQ 1.0, protein RQ 0.81, lipid RQ 0.69).[41] The RQ is theoretically useful in assessing a nutrition regimen, as overfeeding or excessive carbohydrate administration increases $\dot{V}_{CO_2}$ and leads to an RQ $> 1.0$, while underfeeding with associated lipolysis decreases the RQ.[46]

The amount of lean body mass is the primary determinant of REE, but multiple other factors can influence REE (eg, age, sex, presence of fever or inflammation, thyroid function).[63] REE can increase substantially in critically ill patients due to stress-induced metabolic effects, and can fluctuate with the course of the disease process.[41] Sedation, analgesics, and neuromuscular blocking agents reduce REE, while pressors raise REE.[44,64] The magnitude of alteration in REE varies widely between critically ill patients, ranging from hyper- to iso- to hypometabolic, making indirect calorimetry a useful tool to calculate energy needs. Green et al[65] reported energy requirements of 25.6–57.6 kcal/kg/d in mechanically ventilated critically ill patients. It should be obvious that such unpredictability questions the accuracy and practical utility of these equations.

In addition, indirect calorimetry equipment ("metabolic cart") is expensive, requires technical expertise to operate, and is often unavailable in many institutions. It is inaccurate with $F_{IO_2} \geq 60\%$, PEEP $\geq 12$ cm $H_2O$, air leakage in the respiratory circuit (leaking chest tube or endotracheal cuff, bronchopleural fistula), hemodialysis, extreme pain

or agitation, and with calibration errors.[2,66] Furthermore, despite the theoretical usefulness of the RQ in nutrition titration, it has a low sensitivity and specificity as an indicator of over- and underfeeding.[46] A number of confounding factors can increase or decrease the RQ, including acid-base disorders, hypo- or hyperventilation, and body habitus.[2]

More than 200 predictive equations have been published to approximate energy requirements in the absence of indirect calorimetry.[67] However, performance of any one of the equations is jeopardized by extrapolating to a different patient population. The Harris-Benedict equation, the most commonly used predictive equation, was developed in 1919, based on indirect calorimetry values from healthy adults, and uses sex, age, height, and weight to determine basal energy expenditure.[68] In 1979, Long et al[69] proposed modifications to the original Harris-Benedict equation to account for the metabolic fluctuations of critical illness: multiplying the basal energy expenditure by stress and/or activity factors. More recently, several predictive equations have been designed using critically ill patient populations, including those published by Swinamer et al,[70] Ireton-Jones et al,[71,72] and Frankenfield et al.[73,74] A simpler formulaic approach recommended by the American College of Chest Physicians 1997 consensus statement is the use of "kilocalorie per kilogram" (kcal/kg), with energy goals in the critically ill patient population of 25 kcal/kg/d.[75] A range of 20–25 kcal/kg/d is considered an appropriate target for critically ill patients, to avoid over- and underfeeding.[7]

Despite multiple comparative studies, there is no consensus about which predictive equation is most accurate in the critically ill patient[63,67,76,77] or most appropriate to use in the CCI patient. Substantial error, when compared to indirect calorimetry, in the range of 7–55%,[63] predisposes patients to over- and underestimation of energy needs. This is not surprising, as many of the equations are based on static variables, and the critically ill are known to endure wide day-to-day fluctuations in metabolic rates. Many of the studies evaluating predictive equations use data from a single indirect calorimetry measurement, which appears to be inadequate.[78] Another limitation of predictive equations is the failure to account for potential nutrient losses through diarrhea, wounds, fistulas, and hemodialysis, and fluctuations in REE, due to the underlying illness or treatment. Furthermore, there is a lack of randomized controlled studies in this area, with much of the current data from observational studies.[63] It should be noted that, although indirect calorimetry is considered the gold standard against which predictive equations are measured, there is no prospective randomized trial showing improved outcomes with indirect calorimetry, compared to formula-derived regimens.[78]

Another difficulty with energy determinations arises in the obese critically ill patient. Whereas an accurate weight is often difficult to obtain in the ICU, due to fluid shifts and the use of bed scales, the question of which weight to use in predictive equations for the obese patient is even more complex. Body composition consists of fat mass and fat-free mass (primarily composed of body cell mass), the last of which is the metabolically active component that predominantly contributes to REE.[79] The concern is that use of the actual body weight (ABW) in the obese would overestimate energy needs, as much of the excess weight is metabolically inactive and lead to overfeeding, while ideal body weight (IBW), as calculated by the Hamwi formula,[80] would underestimate requirements. In practice, adjusted body weight (AjBW) is frequently used in the obese population:

$$\text{AjBW} = \text{IBW} + [(\text{ABW} - \text{IBW}) \times \text{correction factor}]$$

where the correction factor is a value between 0.25–0.50.[78] The AjBW is criticized by some as not being based on sound research, with some practitioners preferring to use ABW or IBW with one of the predictive equations.[79] There is no consensus approach at this time.

Given the frequent unavailability of and difficulties associated with indirect calorimetry, the lack of consensus approach in regard to the use of predictive equations, the complex interplay of factors affecting REE in the CCI patient, and a propagation of errors regardless of which method is used, our approach has been to target 20–25 kcal/kg adjusted dry weight/d. For the future, we envision a more robust metabolic assessment methodology in CCI, consisting of the following attributes: determination of the relative REE per kilogram of body cell mass, incorporation of this information into a composite score that incorporates other clinical and biochemical parameters, a 2 time-point process to determine a nutrition risk score based on response to therapy within the first 1–2 weeks of CCI care, and, finally, validation in the CCI patient population. Based on this metabolic risk tool, CCI patients can be accurately stratified to better guide decision-making regarding care plans.

### Evidence Base for Nutrition Support in CCI

There are virtually no data available on nutrition support specifically in the CCI patient, so this section will focus on important studies involving ICU patients, many of whom experience prolonged critical illness (PACI + CCI patients).

Extensive data support the use of enteral nutrition (EN) as the primary mode of nutrition support in patients with a functional gastrointestinal tract.[15,81] EN is associated with

a relatively low cost and complication rate, and provides a trophic stimulus to enterocytes, possibly reducing bacterial translocation.[82] Providing EN early can favorably modulate the immune and catabolic responses, preserve gastrointestinal integrity, and support wound healing.[83] The gastrointestinal mucosal barrier, harboring large amounts of immune cells, is disrupted with starvation, allowing bacteria or their antigens to enter the circulatory or lymphatic systems.[84]

In many patients, relying on EN alone results in underfeeding, due to inadequate tolerance of feeds and frequent nil per os status for procedures or ventilator weaning trials. Kemper et al[85] determined that in a small group ($n = 22$) of mechanically ventilated postoperative patients, those receiving EN alone achieved an average of 68% of caloric requirements, while those receiving parenteral nutrition (PN) alone or in combination with EN received 80% of required energy. Other observational studies have confirmed the frequency of underfeeding with EN, with mean amounts of received calories as low as 52%,[86] and as few as 43% of patients ever achieving goal nutrition.[87]

Combining PN and EN to reach target calories was studied in 5 randomized controlled trials (RCTs) between 1987 and 2000, but before tight glycemic control in the ICU was routine. A meta-analysis of these RCTs demonstrated no effect of combined EN/PN on mortality, infectious complications, hospital stay, or days on mechanical ventilation.[88] However, with the current landscape of tight glycemic control coupled with central line associated bacteremia (CLAB) prevention protocols, infectious risk associated with central lines has been dramatically reduced.[89] Therefore, the paradigm of combined modality EN/PN to assure adequate nutrition and prevent underfeeding-associated catabolism still seems rational and should be reexplored.[90]

Average energy intakes of critically ill patients are reported at 49–70% of calculated requirements,[91] consistent with a general trend toward underfeeding. Nutrition can be classified according to the proportion of the REE supplied: hypocaloric (0.5–0.9 × REE), isocaloric (1.1–1.3 × REE), and hypercaloric (> 1.5 × REE).[52] As the understanding of the deleterious effects of hypercaloric feeding (ie, overfeeding) became apparent, reductions in the amount of prescribed calories from hyper- to isocaloric became the standard of care.

Several relevant observational studies have been performed. Rubinson et al[48] performed a prospective cohort study of medical ICU patients (≥ 96 h in the ICU), determining percent of recommended calories delivered based on American College of Chest Physicians (ACCP) guidelines (25 kcal/kg/d). Patients receiving ≥ 25% of their caloric goal had a significantly reduced risk of bloodstream infection, when compared to those receiving < 25% (relative hazard 0.24, 95% CI 0.10–0.60). Villet et al[43] prospectively studied 48 surgical ICU patients (PACI and CCI), calculating weekly caloric balance (calories received minus calories targeted), and found an association of cumulative energy deficit with increased number of total and infectious complications, length of mechanical ventilation, and ICU stay. Importantly, a multiple regression analysis showed that energy debt accumulated at the end of the first week (5,000–9,000 kcal) was a strong determinant of poor outcome.

Krishnan et al[92] studied a prospective cohort of 187 ICU patients, categorizing them by tertiles of achieved caloric intake (ACCP goals). Patients in the highest tertile (≥ 66%) were less likely to be discharged from the hospital alive compared to the lowest tertile (≤ 33%). Those receiving 33–65% of goal (9–18 kcal/kg/d) were most likely to be weaned from mechanical ventilation in the ICU. Another observational study by Stapleton et al[93] looked at tertiles of intake with outcome and found an association of greater caloric intake with longer ICU and hospital stay, but no association with mortality.

Hise et al[94] made note that prior studies of nutritional intake neglect to quantify incidental kcal received through intravenous dextrose and lipid-based sedatives (eg, propofol). This group performed a prospective cohort study of 77 critically ill patients (in ICU ≥ 5 d), accounting for calories received outside of nutritional therapy. They found an increased ICU stay (24 vs 12 d) with ≥ 82%, compared with < 82% achieved calories (goal kcal 25–35 kcal/kg/d).

Combined, these observational studies support an optimal dose of EN that is 25–66% of goal calories (about 9–18 kcal/kg/d) in ICU patients to optimize outcome and avoid harm.[91,94] However, a possible bias in these studies is that more severely ill patients are less likely to tolerate or receive uninterrupted EN and more likely to require a longer ICU course with more complications.[91]

In sum, the above data are not convincing with respect to optimal nutrition support in the CCI patient. This means that CCI physicians need to exercise rational decision-making with close monitoring and poise to adjust their nutritional prescriptions with any indications of detrimental under- or overfeeding. In other words, we recommend "dialoguing" with the patient's metabolism by assessing and reassessing the response to nutritional therapy, rather than dictating an immutable, a priori prescription.[36]

### Our Approach to Nutrition Support in CCI

Our current approach to nutrition support in the CCI population is based on theory, available outcome data from the ICU, and extensive clinical experience caring for CCI patients in the respiratory care unit (RCU) at the Mount Sinai Hospital (MSH). The philosophy of our team approach to CCI merits a brief discussion. Our team developed metabolic support protocols for CCI in the late 1980s

and has regularly modified these protocols based on a variety of patient care end points (individual patient responses, clinical performance of the MSH-RCU, nursing care feedback, hospital administration constraints, and published IRB-approved clinical research studies—both observational and interventional). The MSH-RCU team consists of a pulmonologist (primary physician), dedicated metabolic support team (endocrinology attending physician and fellow-in-training), nurse practitioners, staff nurses, and other consulting services, including palliative care. As a result of a consistent team structure and stable protocol management for over 20 years, the MSH-RCU team functions at an intuitive level where all members are able to recognize shared problems and be familiar with the likely responses. This dramatically improves response times and, in theory, facilitates efforts to dissipate allostatic overload and improve the chances for successful liberation from mechanical ventilation—the primary end point.

Assessment and initiation of nutrition support when needed should take place early in the ICU stay, before admission to the MSH-RCU, to attenuate allostatic load. This would be expected to lessen the severity of CCI. However, once a patient is transferred to the MSH-RCU, nutrition support is initiated immediately.

One primary goal of nutrition support in the MSH-RCU is to provide sufficient protein to compensate for hypercatabolism. Protein should be provided initially in amount of approximately 1.0–1.2 g/kg/d and then uptitrated to 1.2–1.5 g/kg/d, depending on biochemical tolerance (blood urea nitrogen [BUN], UUN, and ammonia) and clinical requirements (wounds, body composition, organ function, etc). This is consistent with the 1997 ACCP consensus statement recommending 1.5 g/kg/d of protein and 20–25 kcal/kg/d total energy.[75]

Patients with additional routes of nitrogen loss, including renal replacement therapy,[95] a decubitus ulcer, or high output ostomy, may also require increasing protein, sometimes as high as 2 g/kg/d, evaluated on a case-by-case basis.

Another primary goal of nutrition support in the MSH-RCU is to provide sufficient energy, as non-protein calories (ie, carbohydrates and lipids), to compensate for hypermetabolism, and if inflammation is somewhat quelled, possibly protein-sparing. Whereas some controversy exists as to the superiority of hypocaloric (9–18 kcal/kg/d) versus isocaloric (20–25 kcal/kg/d) nutrition early in the ICU stay (ACI), a direct extrapolation to the CCI population is not substantiated. In fact, from an intellectual standpoint, the titration of nutrients in the CCI must still be impressionistic; there are simply too many errors in assumptions and metrics that are propagated in clinical management for reliance on any single set of rules. Additionally, there are essentially no CCI interventional clinical trials to formulate an evidence-based decision, and, in theory, virtually all of the allostatic overload mechanisms are non-Darwinian and cannot be extrapolated from Darwinian physiology with great certainty. Therefore, based on our experience with empirical management in the MSH-RCU, calorie goals for the CCI population should be set at 20–25 kcal/kg dry adjusted weight/day. This is comparable with other expert opinions: 11–14 kcal/kg/d of ABW or 22–25 kcal/kg/d of IBW.[42]

The route, type, and formulation of nutrition support in CCI are guided by various protocols in MSH-RCU. Nutrition is provided primarily via the enteral route. Semi-elemental feeds, containing hydrolyzed protein, are preferred over whole protein formulas in the CCIS population. This type of EN has been associated with improvements in diarrhea and visceral protein stores, and a shorter hospital stay in trauma and critically ill patients.[96–98] Elemental feeds, containing only free amino acids, are hypertonic, but, in our experience, when diluted can provide an effective temporizing measure to provide trophic EN without diarrhea. Choosing the optimal EN formula should include consideration of fluid and sodium status (concentrated vs dilute semi-elemental formula), glycemic status (standard vs low carbohydrate semi-elemental formula), and renal status (low potassium/magnesium/phosphorous semi-elemental vs whole protein renal formulas). Routine use of "diabetes" or "pulmonary" formulas in mechanically ventilated patients with low-carbohydrate, high-fat, and fiber content in an effort to decrease $\dot{V}_{CO_2}$ from carbohydrate oxidation may cause delayed gastric emptying.[2]

The use of immune-enhancing enteral formulas, supplemented with glutamine, arginine, nucleotides, or an increased $\omega$-3:$\omega$-6 fatty acid ratio, has been studied in critically ill patients. Results of these studies ranged from reduced requirements for mechanical ventilation,[99] to no effect,[100] to increased mortality in patients with sepsis.[101] Some studies have confirmed benefits of eicosapentaenoic acid (EPA), $\gamma$-linolenic acid (GLA), and antioxidants in patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI).[102,103] In contrast, the recently published OMEGA study,[104] a randomized, double-blind, placebo-controlled trial of 272 patients with ALI, showed no benefit in clinical outcome and possible harm with enteral $\omega$-3 fatty acids, GLA, and antioxidants, compared to an isocaloric control. The study population demonstrated significantly fewer ventilator-free days and more days with diarrhea. Use of immune-enhancing EN formulas in the CCI population requires further study and is not routinely recommended.

Enteral nutrition is provided initially through a nasogastric feeding tube. Patients should have the head of the bed elevated by about 40° with gastric feedings; many times this angle is underestimated by casual visual inspection at the bedside. Patients at high risk of aspiration or with poor tolerance of gastric feeding may have a nasojejunal tube

placed. If EN is required for a prolonged period of time (> 30 d), a percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ) should be performed. Jejunal feedings may be associated with improved EN tolerance and a reduced rate of complications.[105] The routine placement of post-pyloric enteral access has gained favor in recent years, but implementation of this concept has more to do with institutional culture (availability of experts and willingness to place and monitor the device) than scientific evidence. In CCI, EN is initially provided continuously, but can alternatively be cycled overnight or provided in boluses to facilitate physical therapy or other needs.

If caloric goals cannot be met with EN, or are not anticipated to be met with EN (intolerance, procedural interruptions, or other logistical factors), PN should be added for combined modality nutrition support. Combined protein and energy requirements and monitoring strategies are unchanged using combined modality nutrition support. Hyperglycemia is avoided with the use of intravenous insulin in the PN proportioned to the amount of dextrose in the PN (0.1 units/g initially) and then titrated to goal. Subcutaneous insulin may be continued to be proportioned to the amount and schedule of carbohydrate in the EN, if still being used. Amounts of electrolytes, volume, and micronutrients are formulated based on patient specific parameters.[36] For patients on hemodialysis, use of intradialytic PN (IDPN) may be considered to supplement inadequate EN and compensate for hemodialysis-related protein-energy losses, but is not considered as an adequate sole source of nutrition, due to limited amounts of nutrients received at each hemodialysis session.[95,106]

CCI patients in the recovery phase should have a swallowing evaluation to determine the safety of oral feeding. A dysphagia diet is usually indicated to prevent aspiration, as swallowing dysfunction is common secondary to the effects of intubation and tracheostomy. CCI patients tolerating oral feeding should have a calorie count performed to assess intake with appropriate reductions in EN made. Once patients can meet calorie targets solely through the oral route, nutrition support is withdrawn.

### Monitoring Nutrition Support in CCI

An important aspect of providing quality nutrition support involves close follow-up and monitoring of tolerance to the regimen. A number of clinical and biochemical variables should be followed, with adjustment of the nutrition regimen to maximize benefit while avoiding iatrogenesis. Facile rule-sets are devised in the MSH-RCU so any member of the team can recognize a potential nutrition/metabolic problem, report, and implement the response in an expedited fashion.

Weights should be monitored on a regular basis, but with the understanding that fluctuations may often be due to edema or diuretics rather than change in lean body mass. Recording of "I"s and "O"s and attention to the patient's fluid status on physical exam may help in this interpretation. Similarly, serum albumin and prealbumin should be followed, but with an understanding that they may not directly reflect nutritional status, but instead are markers of inflammation and hepatic function.[19,54] Hypophosphatemia is common and indicates refeeding syndrome and/or vitamin D deficiency. Phosphate should be repleted in either case, enterally or parenterally. If refeeding syndrome is suspected, then carbohydrate should be limited until the phosphate levels have stabilized.[53] Vitamin D should be started in all cases of hypophosphatemia, due to the high prevalence of this deficiency among all hospital patients and particularly among CCI patients.[28]

Careful attention should be paid to signs of overfeeding, with timely reduction of nutrients when indicated. To fine-tune protein intake, BUN should be regularly monitored with expected small increases. Clinically important elevations in BUN (> 70 mg/dL) or ammonia (> 70 $\mu$g/dL) should prompt a reduction of protein and/or increase in hydration.[6] Nitrogen balance can be periodically measured in an effort to avoid underfeeding of protein:

$$\text{Nitrogen balance} = ([\text{grams daily protein consumed}/6.25] - [\text{UUN}/\text{d} + 4])$$

Results may be invalid with liver and renal disease causing nitrogen retention or via extra-renal losses (severe diarrhea, wounds).[2] In addition, the contribution of urea to total urinary nitrogen declines with increased inflammation. As a result, nitrogen balance determinations are fraught with error and should be interpreted correctly. Hyperglycemia is monitored closely, since the evidence base is compelling that glycemic control impacts outcome. Abnormal average glucose levels as well as glycemic variability should be addressed with reductions in calories from dextrose and/or increasing doses of insulin, or a substantial change in the nutrition support delivery system altogether. Liver function tests (LFTs) should be monitored for cholestasis or transaminitis. If present, nonprotein calories should be reduced, iatrogenesis (medications) considered, and, if persistent, appropriate consultations requested.

When using EN, daily tolerance of feeds should be assessed, including signs of abdominal distention, pain, vomiting, and diarrhea. Gastric residuals should be monitored but tolerated up to 500 mL.[42] A lower threshold for holding EN based on gastric residuals typically results in underfeeding. Prokinetic agents should be used to facilitate EN tolerance, and, when appropriate, consideration should be made for post-pyloric feeding access.

Diarrhea affects approximately one third of all critically ill patients[107] and is extremely common in the CCI population. Causes include malnutrition-induced gut edema, sorbitol-containing or high osmolarity medications, infection such as *Clostridium difficile*, stool impaction, or intolerance to a specific enteral formula.[2] Diarrhea results in malabsorption of nutrients and dehydration and predisposes to skin breakdown. Empiric therapy with bismuth/salicylate added directly to feeds (10–30 mL/500 cc bag) may be initiated.[5] This maneuver is not evidence-based, but has been successful in our experience with CCI patients. Potential for gastric irritation and bleeding with chronic use should be noted. If needed, 4 g of cholestyramine 2–3 times daily can be added to adsorb intraluminal toxin with gut dysbiosis. The use of pre-biotics (inulin, oligofructosaccharides) or pro-biotics (*Bifidobacterium*, *Lactobacillus*) may be considered for patients with recurrent *C. difficile* infection, but available evidence on this practice is still inconclusive. If tolerance to semi-elemental feeds cannot be accomplished with the above methods, a trial of diluted elemental feeding can be tried.[6] If goal calorie targets cannot be reached despite all efforts to improve diarrhea, then PN should be added. This entire diarrhea management plan must be expedited. This is an important point, as subjective delays can have an important impact on the clinical course of CCI, especially when liberation from the ventilator is hoped for within a period of days to weeks, and not weeks to months.

The paradigm of "bridge PN" has not been substantiated in the critical care literature, but close scrutiny reveals that the study parameters did not investigate CCI patients, use tight glycemic control, or formulate low-infectious risk PN. This last point (low-risk) deserves further explanation. Many times, the culture of a nutrition support team is biased by the experiences of members of the team and the pertinent literature. We have used lipid-free ("2-in-1") PN often and specifically for instances of short-term bridge therapy, until enteral access is (re)placed or tube feeds tolerated. Though benefit has not been demonstrated (perhaps due to high beta-error in relatively small studies), risk is virtually nil compared with a dextrose-based maintenance intravenous fluid. Furthermore, decisions regarding appropriateness and composition of PN are managed by an experienced nutrition support team. The economic impact has not been analyzed, but the incremental cost compared with tube feeds or an extra day in the RCU is not expected to be substantial. Therefore, our practice in the MSH-RCU has been to provide uninterrupted nutrition support using bridge PN when needed, and our experience with this has been overwhelmingly favorable. Needless to say, this is still an impressionistic maneuver and does require scientific validation. The proof-of-concept study here would be to demonstrate whether protein-sparing (anti-catabolic) and pharmacologic effects of intravenous amino acids, dextrose, and micronutrition exist and confer relevant clinical outcome benefit.

## Metabolic Control

Hyperglycemia is prevalent in CCI. Van den Berghe et al[26] identified hyperglycemia, defined as blood glucose (BG) $>$ 110 mg/dL, in 98.7% of a cohort of cardiovascular surgery patients, most of whom had PACI. Frequently, the etiology is stress hyperglycemia in patients without a prior diagnosis of diabetes mellitus (DM), but hyperglycemia can also occur in patients with preexisting type-1 (T1DM) or pre-existing or occult type-2 DM (T2DM).

In recent years, a paradigm shift has occurred regarding optimal glycemic control in the critically ill patient. The traditional view regarded hyperglycemia merely as marker of disease, with stress-induced hyperglycemia as an adaptive and beneficial response, ensuring availability of glucose to support organ function during stress.[108] BG values as high as 200–215 mg/dL were deemed physiologic and tolerated, with glucose lowering measures undertaken only for higher values, to prevent obvious harmful effects such as glucosuria with associated fluid shifts.[109]

The proof-of-concept well controlled Leuven study by Van den Berghe et al[26] challenged the traditional notion of "adaptive hyperglycemia" and introduced tight glycemic control (or metabolic control) to ICU practice. In this prospective RCT, 1,548 surgical ICU patients were randomized to receive intensive insulin therapy, targeting BG 80–110 mg/dL, or the traditional approach (BG $<$ 215 mg/dL). All patients were concurrently managed with a nutrition support protocol consisting of early EN with the addition of early PN as needed to reach goal nutrition. The intervention group not only showed a reduced mortality at 12 months (4.6% vs 8.0%, $P < .04$), but also reduced rates of acute kidney injury, sepsis, hyperbilirubinemia, anemia, need for PMV, and critical illness polyneuropathy. Mortality benefits were maintained in a 4-year follow-up study as well.[110] The same intervention studied in a Leuven medical ICU population ($n = 1{,}200$)[27] also resulted in reductions in morbidity (acute kidney injury, prolonged ventilator weaning) and a reduced ICU stay, but did not significantly reduce mortality. Among patients who remained in the ICU $\geq$ 3 days (a PACI group), in-hospital mortality was reduced in the group with tight glycemic control (52.5% to 43.0%, $P = .009$).

A number of mechanisms explain the benefits of tight glycemic control in the critically ill, including prevention of hyperglycemia and direct insulin effects. Stress-induced hyperglycemia is stimulated by cytokine- and hormone-mediated inductions of insulin resistance with superimposed impairment in glucose uptake mechanisms (GLUT-transporters).[111] Hyperglycemia is associated with pro-inflammatory effects, oxidative tissue injury, endothelial

dysfunction, and pancreatic ß-cell apoptosis.[25,110] Morbidity associated with hyperglycemia includes increased rates of nosocomial and wound infection, and impaired wound healing.[112,113] Insulin corrects hyperglycemia but also suppresses production of reactive oxygen species via effects on nuclear factor-$\kappa\beta$ (NF-$\kappa\beta$), acts as a vasodilator through generation of nitric oxide, and exerts anabolic effects, which may attenuate catabolism.[114] A multivariate logistic regression analysis of the Leuven results showed that BG control, and not the insulin dose, explains most of the beneficial effects of tight glycemic control on outcome.[115]

Subsequent to the Leuven studies, other centers attempted to replicate these outcomes in smaller, less controlled clinical trials, but failed to show a mortality benefit.[116–118] Most notable among these studies is the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study.[119] In this multicenter RCT, 6,104 mixed (medical/surgical) ICU patients were randomized to receive tight glycemic control (BG 80–108 mg/dL) or a moderate glycemic control (BG 140–180 mg/dL). Results showed an increased mortality and a 13-fold increase in the incidence of severe hypoglycemia (BG $<$ 40 mg/dL) in the tight glycemic control group.

Whereas following the Leuven studies, ICUs began to implement tight glycemic goals, results of the NICE-SUGAR data led many to question the safety of intensive insulin therapy, with relaxation of BG targets to 140–180 mg/dL. However, a thorough investigation of the differences between the studies sheds light on key differences in methodology, with insight on how to better interpret the data. Importantly, the Leuven studies followed European guidelines, instituting early PN when EN was inadequate, while in NICE-SUGAR, PN was withheld the first week. The amount of nutrition received was 19 kcal/kg/d over the first 2 weeks in Leuven, but 11 kcal/kg/d in NICE-SUGAR. Committing to tight glycemic control while simultaneously underfeeding may have explained the high rates of hypoglycemia and poor outcome in NICE-SUGAR.[120] Other fundamental differences in the studies include the method of glucose measurement (blood gas analyzer in Leuven, variety of point-of-care glucose meters in NICE-SUGAR), types of insulin pumps, frequency of monitoring of potassium, and differences in the glucose targets of the control group.[109,121,122]

An important lesson to learn from the Leuven/NICE-SUGAR controversy is the importance of combining intensive insulin therapy with optimal nutrition support to reduce allostatic load while avoiding risk of hypoglycemia.[120] This is the fundamental concept behind IMS.[123,124] Nutrition support and metabolic control are not mutually exclusive; each is not sufficient, but both are necessary.[125] The efficacy of PN as a component of combined modality nutrition support is strengthened by its ability to consistently deliver dextrose without the risk of EN interruptions. Meyfroidt et al[126] reexamined the data from the 2 Leuven studies and noted that rates of EN were much lower in Leuven 2001 (with better mortality outcome) versus 2006 (19% vs 65%). Furthermore, in a logistic regression model, receipt of EN was found to correlate with higher glycemic variability, an independent risk factor for hypoglycemia. Increased glycemic variability has also been increasingly described as a strong independent predictor of mortality in ICU patients.[127,128] Taken together, the IMS paradigm in the CCI model includes the use of combined modality nutrition support, with bridge PN as needed, and metabolic control targeting not only average daily BG but glycemic variability as well.

In the MSH-RCU we use a protocol of multiple daily subcutaneous insulin injections with combinations of rapid, intermediate, and long-acting insulin based on the total daily dose of insulin received, and have been able to safely target 80–110 mg/dL.[6,129] Important protocol modifications that have allowed us to safely implement these concepts include:

- Having a bag of 10% dextrose at the patient bedside for use whenever the tube feeds are stopped (for routine bedside patient care or procedures), to prevent hypoglycemia with insulin "on-board"
- Continuous in-service education of nurses and nurse practitioners on the importance of tight glycemic control, insulin actions, and recognition of significant hypo- or hyperglycemia with appropriate corrective actions
- Brief daytime intensive insulin therapy protocols are implemented when severe hyperglycemia occurs.
- The notion of glucotoxicity: when appropriate up-titration of insulin fails to reduce hyperglycemia, BG levels are managed by concurrently reducing the EN/PN carbohydrate and increasing the insulin.

### Nutrition Pharmacology and Endocrine Support

If nutrition is the interaction between diet and metabolism, then nutritional pharmacology describes the effects of substances, not conventionally regarded as foods, on metabolism. Many of these substances have been demonstrated to have net benefit in critical illness and are used in the CCI setting. Decisions regarding the appropriateness of each substance should be made by an experienced clinician on a case-by-case basis, weighing all relevant risks and benefits. A partial list of these substances will be reviewed here. The majority of the evidence that is relevant for CCI patients is extrapolated from general critical care settings (ACI + PACI + CCI + RCI) or prolonged critical illness (PACI + CCI). The few endocrine and metabolic studies that have been conducted in a dedicated CCI setting are provided in Table 1.

Table 1. Endocrine and Metabolic Studies Performed Exclusively on Chronically Critically Ill Patients

| Topic | Study Design | Subjects, *N* | Findings |
|---|---|---|---|
| Bone | Retrospective | 49 | High prevalence of bone hyper-resorption (92%) and vitamin D insufficiency/deficiency (90%).[28] |
| Bone | Retrospective | 55 | Bone hyper-resorption is independent of parathyroid hormone and suppresses with intravenous pamidronate and calcitriol.[130] |
| Bone | Prospective randomized controlled trial | 20 postmenopausal females | Intravenous ibandronate suppresses bone hyper-resorption; bone hyper-resorption worsens without treatment.[131] |
| Gonadal | Retrospective | 30 males | High prevalence of hypogonadism (96%) using age-adjusted bioavailable testosterone levels.[132] |
| Thyroid | Retrospective | 185 | Mean thyroxine stimulating hormone levels were not associated with clinical outcome.[133] |
| Glycemic control | Retrospective | 59 | Tight glycemic control targeting a blood glucose of 80–110 mg/dL can be achieved safely using subcutaneous insulin.[129] |

### Glutamine

Glutamine is a conditionally indispensable amino acid that may enhance nitrogen retention,[134] gastrointestinal absorption,[135] and immune function.[136] Glutamine levels frequently decrease during critical illness.[137] A number of smaller clinical studies have shown benefits with glutamine supplementation in the critically ill, including decreased stay and mortality, but stronger evidence for routine supplementation is lacking.[138,139] A recent RCT administering parenteral glutamine (20.2 g/d) to critically ill patients found no effect of glutamine on the incidence of new infection when administered up to 7 days.[140] A longer duration may have been required to see a positive outcome, or, alternatively, there may have been benefits other than prevention of "new infection."[141] Potential adverse effects of glutamine include hyperammonemia and azotemia; glutamine supplementation should routinely be accompanied by increases in free water flushes.[6] In the MSH-RCU we provide 15 g/d of glutamine, unless contraindicated.

### Wound Healing

Nonhealing decubiti ulcers are an important problem among CCI patients, and IMS addresses this by providing sufficient nitrogen and metabolic control. However, other nutritional substances can also promote wound healing. Zinc is commonly supplemented for support of wound closure, but little evidence exists supporting this practice in the absence of zinc deficiency.[6] Zinc supplementation may induce a copper deficiency in the setting of inadequate nutrition intake, so injudicious or prolonged use should be avoided.[5] Vitamin C is required for collagen synthesis but has not been consistently linked to improvements in wound healing.[142] Use of a multivitamin supplement in CCI patients is not supported by evidence but is rational and has little down side.[6]

Vitamin A deficiency has been associated with impaired wound healing, particularly in steroid-treated patients.[143] Potential mechanisms include effects of retinoids on fibroblast differentiation, collagen formation, and macrophage inflammation.[143,144] Well designed studies are needed to confirm a benefit of vitamin A supplementation on wound healing, in light of potential toxicities of hypervitaminosis A, including detrimental effects on bone health.[145]

Arginine is also a conditionally indispensable amino acid and is associated with improvement in wound healing and immune function.[146,147] Arginine is obtained in the diet (20–25%), synthesized endogenously via citrulline metabolism in the kidney, and produced through protein breakdown. Arginine is an important intermediate in cell growth and proliferation, wound healing, and nitric oxide production, and is involved in lymphocyte differentiation.[148] Requirements for this amino acid increase with critical illness, and, thus, supplementation has been considered for possible therapeutic benefits. Supplementation with 6–9 g/d of arginine may facilitate wound healing when conventional therapy is ineffective.[146,147] One concern with arginine supplementation is increased generation of nitric oxide, with resultant excessive vasodilation and hypotension.[148] Further research is needed to clarify the safety and efficacy of arginine supplementation for CCI patients.

In the MSH-RCU, CCI patients with wounds that are not healing well despite target nutrition support and metabolic control are supplemented with enteral zinc sulfate 220 mg twice a day, vitamin C 500 mg twice a day, and a multivitamin once a day, and then re-evaluated in 2 weeks.

### Bone and Mineral Metabolism

The CCIS frequently manifests impaired bone health and abnormal mineral metabolism. Metabolic bone disease, characterized by bone hyper-resorption with elevated urine N-telopeptide (NTx), has been identified in 92% of

CCI patients.[28] Loss of bone during critical illness may be difficult to reverse and predisposes to osteoporosis, fracture, and worsened quality of life for those CCI patients who recover. A recent retrospective cohort study of patients requiring intensive care and mechanical ventilation $\geq$ 48 hours showed an increased risk for sustaining an osteoporosis-related fracture in postmenopausal female study patients, compared to population-based controls (hazard ratio 1.65, 95% CI 1.08–2.52, $P = .02$).[149] This latest clinical outcome finding supports our longstanding MSH-RCU aggressive approach to concurrent bone health management in CCI patients.

Multiple factors contribute to bone loss: cytokine-mediated effects; immobilization; vitamin D undernutrition and secondary hyperparathyroidism; neuroendocrine abnormalities; and medications.[150] Elevated levels of cytokines, especially TNF-$\alpha$, IL-6, and IL-1, promote osteoclastogenesis via stimulation of receptor activator of NF-$\kappa\beta$ ligand (RANKL) secretion by bone stromal cells and lymphocytes.[151] Immobilization is a known inducer of bone hyper-resorption, as seen in spinal cord injury patients, and may precipitate hypercalciuria, hypercalcemia, and nephrolithiasis.[152] Vitamin D insufficiency/deficiency is common in CCIS, found in 90% of CCI patients in one cohort.[28] Immobilization, with associated calcium efflux from bone, can lead to suppression of parathyroid hormone (PTH), while secondary hyperparathyroidism can result from vitamin D undernutrition. Nierman and Mechanick[28] showed that of 45 CCI patients with elevated urine NTx, 42% had elevated PTH levels consistent with predominant vitamin D deficiency, 9% had a suppressed PTH consistent with predominant immobility-induced resorption, and 49% had normal PTH levels consistent with a mixed etiology. Several hormonal changes seen in CCI, including hypercortisolism and low levels of IGF-1, age-adjusted bioavailable testosterone, and T3 have known effects on bone turnover, favoring resorption over formation.[153,154] Medications commonly used in CCI patients, including corticosteroids, heparinoids, and loop diuretics, adversely affect bone health as well.[6]

Combined therapy with adequate vitamin D, replacement of calcium losses, and judicious use of second generation bisphosphonates have shown promising results in the CCI patient to attenuate bone hyper-resorption. Nierman and Mechanick[130] performed a retrospective study of the use of calcitriol plus pamidronate (90 mg) versus calcitriol alone in CCI patients with documented hyper-resorption, and found significant decreases in urine NTx only with combination therapy. The bone protective effect lasted 18 days. A prospective, double-blinded, placebo controlled trial, the first published RCT exclusively in CCI patients, studied the use of ibandronate (3 mg) versus placebo in 20 postmenopausal female CCI patients.[131] All patients received ergocalciferol (2,000 international units daily), calcium carbonate (1,250 mg daily), and calcitriol (0.25 $\mu$g daily). The ibandronate group showed a 34% reduction in serum C-telopeptide (CTx) (a serum marker of osteoclast function), compared with a 13% increase for the control group on day 6 after therapy ($P = .01$), with no significant effects on osteocalcin (a serum marker of osteoblast function). The effect was no longer present at day 11, indicating a short-term effect of therapy. Possible explanations for the abbreviated effect include an insufficient dose or a protein binding defect, due to hypoalbuminemia. The lack of suppression of osteocalcin with decreasing CTx reflects an uncoupling of resorption and formation seen in CCI bone disease. Importantly, no adverse events associated with bisphosphonates were seen, including fever, hypocalcemia, hypophosphatemia, new-onset atrial fibrillation, or most importantly, acute kidney injury. This RCT was also important because it demonstrated that withholding bisphosphonate treatment (the control arm) in CCI patients was associated with worsening of bone hyper-resorption (increased CTx).

It is our current practice in the RCU to routinely supplement CCI patients with ample calcium to replace losses (1,000–1,500 mg elemental calcium), ergocalciferol to replenish stores of 25OH-D (2,000 international units daily), and calcitriol to circumvent impaired renal 1-$\alpha$ hydroxylase with PTH suppression due to immobilization (0.25 $\mu$g daily). We continue to provide ergocalciferol even in patients with impaired renal 1-$\alpha$ hydroxylase activity, based on the premise that this vitamin D precursor has pleiotropic actions, particularly with the immune system.[155] Calcium and vitamin D supplements are withheld for patients with hypercalcemia, hypercalciuria, and hyperphosphatemia. Dosing adjustments may be necessary to maintain 25OH-D $\geq$ 30 ng/mL. Urine NTx is routinely measured, and when indicative of hyper-resorption, pamidronate 90 mg is administered intravenously once over 4 hours, after at least 3 days of vitamin D replacement to prevent hypocalcemia and hypophosphatemia. With a creatinine clearance $<$ 30 mL/min, the pamidronate dose is decreased to 60 mg (or 1 mg/kg if less than 60 kg dry adjusted body weight) and given over 6 hours. Patients on hemodialysis with evidence of hyper-resorption and no indication of adynamic bone disease (an elevated serum CTx, appropriately elevated PTH, and normal to elevated osteocalcin argue against adynamic bone disease) are given pamidronate 90 mg on the day prior to scheduled hemodialysis.[150] Patients who present to the MSH-RCU with frank hypercalcemia or hypercalciuria, not already on calcium and/or vitamin D, are treated with pamidronate, without pretreatment calcium or vitamin D. Once the urinary and/or serum calcium levels normalize, then calcium and vitamin D are introduced. Fever is common with intravenous pamidronate,[156] and therefore if the patient has a

fever already, then intravenous pamidronate is deferred until the underlying febrile episode is resolved.

As a result of routine PTH-D axis screening in the MSH-RCU, several new cases of primary hyperparathyroidism are detected each year. We have had nearly uniform success in normalizing serum calcium levels in these cases, using cinacalcet therapy (unpublished results).

**Hypothalamic-Pituitary Axes**

Impaired GH-IGF-1 activity contributes to the wasting and catabolism of CCI, suggesting that replacement with recombinant human GH (rhGH) may be advantageous.[13] However, in 2 large parallel RCTs of patients with PACI (total $n = 532$), Takala et al[157] demonstrated an excess morbidity and mortality in the treatment group, despite improved nitrogen balance. A possible explanation for the negative outcome relates to the supra-physiologic doses used, due to the incorrect assumption that GH resistance persists in the chronic phases of critical illness. Furthermore, insulin resistance and hyperglycemia resulting from GH therapy, combined with inadequate metabolic control, may have contributed to toxicity and negated other potential benefits of therapy.[13] Routine use of rhGH is therefore not advised in the CCI patient.

Hypogonadism is commonly seen in CCI patients and may contribute substantially to muscle wasting.[132] Potential benefits of testosterone replacement include improved nitrogen retention, strengthening of skeletal and respiratory muscles, raised hematocrit, improved bone density, and wound healing.[158] There have been no large randomized studies of testosterone replacement in CCI patients; however, review of the literature on hypogonadism in critical illness leads to the conclusion that there may be net harm with androgen therapy.[35] Consideration for therapy in the MSH-RCU is considered on a case-by-case basis in the RCI stage, after consideration of the catabolic rate (UUN), fluid status, cardiovascular risk, liver function, hematocrit, and prostate specific antigen (which is generally elevated due to chronic indwelling urinary catheters). Oxandrolone, an oral anabolic agent, has been shown to attenuate losses of lean body mass and bone mineral content in severely burned patients,[159] but was associated with negative outcomes in the critically ill population and cannot be routinely recommended in CCI.[160]

CCI patients admitted to the MSH-RCU are routinely screened for thyroid dysfunction, as hypothyroidism can impede weaning from the ventilator. True hypothyroidism is suspected by the presence of an elevated TSH. When the TSH elevation is only mild, true hypothyroidism should be differentiated from a resolving nonthyroidal illness syndrome (NTIS), which can also have a mild TSH elevation.[158] Our approach is to check an anti-thyroid peroxidase (TPO) antibody titer, and, if elevated, along with a repeat TSH that is continuing to rise, treatment with levothyroxine is initiated. Alternatively, treatment of NTIS with levothyroxine or liothyronine (T3) is controversial and requires further study.[14,23] In a retrospective study of CCI patients, mean TSH did not differ significantly between those weaned from mechanical ventilation or survived to hospital discharge versus those who did not.[133] Patients receiving EN who require thyroid hormone replacement should have feeds cycled over 20–23 hours, to permit delivery of levothyroxine (midway when TF cycles off) to enhance absorption. If the gastrointestinal tract is nonfunctional or uncertain, intravenous levothyroxine can be administered at 50–80% of the usual enteral dose.[158,161] We have frequently observed that hypothyroid CCI patients, who also have a component of NTIS by virtue of their chronic illness, may exhibit a brief (1–2 week) rise in the TSH with levothyroxine treatment before the TSH physiologically suppresses due to negative feedback.

Critically ill patients commonly receive high doses of glucocorticoids for treatment of an underlying disease process, and are often on tapering doses while in the RCU. Steroid dose reductions should not be more frequent than every 3–5 days, to avoid potential negative effects on respiratory muscles due to secondary adrenal insufficiency.[158] Unexplained hypotension, hyponatremia, hyperkalemia, and hypoglycemia should prompt evaluation for primary adrenal insufficiency. When a patient is admitted to the MSH-RCU on single daily dose glucocorticoid, we routinely split the dose to every 12 hours to facilitate synchronization with the insulin therapy and tight glycemic control. In addition, frequently a patient (typically on hemodialysis) is admitted to the MSH-RCU who cannot be tapered down on their glucocorticoids due to hypotension. We have had many successes using midodrine (2.5–10 mg enterally, 3 times a day) in these cases[162] and suspect that many CCI patients develop a hypoadrenergic dysautonomia.

Administration of hypothalamic-releasing factors is a potential means of correction of the abnormal neuroendocrine function characteristic of CCI. Van den Berghe et al[163] performed a small RCT ($n = 33$) administering GH-releasing peptide-2 (GHRP-2), thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH) in various combinations, compared to placebo, in primarily CCI male patients. Administration of all 3 hormones resulted in reactivation of the GH, TSH, and LH axes. Treatment with releasing factors instead of pituitary or peripheral hormones has the potential benefit of allowing the body to adjust target hormone levels as needed to prevent overdose and toxicity.[163] This intervention should be considered still investigational, and larger studies are needed to clarify the role of hypothalamic-releasing factors in the treatment of CCI patients.

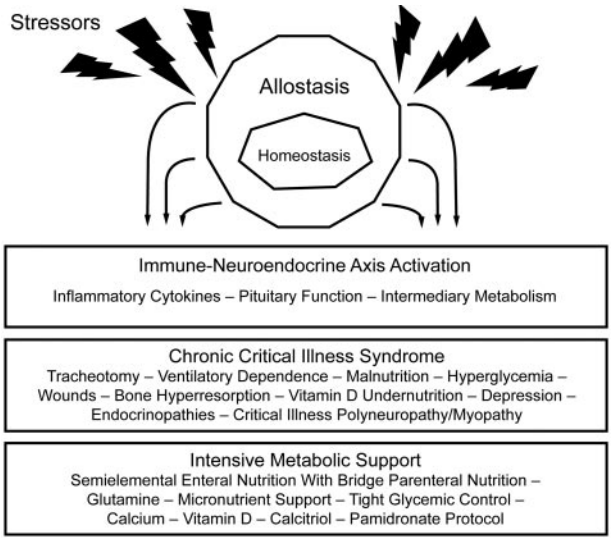


Fig. 2. Overview of effects of allostasis on the immune-neuroendocrine axis and chronic critical illness syndrome. Intensive metabolic support is tailored to address the various components of chronic critical illness syndrome.

## Summary

CCI is not a natural disease, but rather a product of medical technology. CCI has emerged as an important problem in hospital medicine, and successful management strategies will most likely depend on a substantial paradigm shift. The difficulties in definition and diagnosis, particularly differentiation between a fulminant CCIS and forme fruste PMV, may be conceptualized by subsuming both in a CCI framework. That is, a multisystem CCIS ("Type-1 CCI") results from failure to down-regulate the INA, consequent allostatic overload, and loss of chaotic biorhythms. Treatment for this group involves comprehensive IMS (Fig. 2). Whereas, single- (or oligo-) system PMV ("Type-2 CCI") results from failure to liberate from mechanical ventilation due to neuromuscular or other anatomical reasons, even though the INA has appropriately down-regulated and the allostatic state has near-normalized, normal chaotic biorhythms have reappeared and limited IMS protocols can be implemented.

In the MSH-RCU this approach is a meticulous and sometimes tedious activity requiring all stakeholders to participate to realize tangible benefit. Successful MSH-RCU CCI patient outcomes relating to stay and weaning have been reported using our care model, which incorporates a dedicated, institutional metabolic support consultative service.[33,164] At our institution the metabolic support rotation is a critical part of the endocrinology fellowship program, and graduates have experience and expertise in this area. It is hoped that as more physicians are trained in the specialized nutrition and metabolic care of the CCI patient, a critical mass can be realized where all CCI patients, nationally and beyond, can achieve successful outcomes.

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## Discussion

**MacIntyre:** I would like your comments on the recent ARDS Network study on early versus late nutrition: the EDEN trial.[1] There is concern in ARDS that enteral nutrition is the better way to go, but that the timing of providing enteral nutrition is unclear. Aggressive nutrition provides metabolic fuel, but there is concern about bubbling up of gastrointestinal contents and aspiration and making the ARDS worse. So there is a controversy about early aggressive therapy and taking the risk of pneumonia versus trickle feeds that protect the lung. After 1,000 patients in the EDEN trial it turned out that for at least 7 days both strategies had similar outcomes. How would that fit into your algorithm of being less aggressive metabolically for up to 7 days in order to protect the lung?

1. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307(8):795-803.

**Mechanick:** First, in theory, there are a lot of factors that figure into how you approach nutrition. One of them is a psychological barrier on the part of medical and paramedical personnel against the use of parenteral nutrition because of a fear of complications, primarily infectious, hepatopathy, and hyperglycemia. Most parenteral nutrition in this country is still directly managed by non-physicians.

I'm involved in several organizations where we're trying to address the national shortage of physician experts in nutritional medicine. Most providers will generally manage parenteral nutrition based on "numbers": for instance, you must provide 25-30 calories/kg per day, 60-70% carbohydrates, etc, and *then* manage the repercussions or complications of this intervention. This approach is too simplistic and has intrinsic hazards. It's not surprising that this approach would confer an adverse effect in your patient population.

Now let's look at enteral nutrition. One of the problems with enteral nutrition is that by finessing it in a patient with uncertain gastrointestinal

function (because parenteral nutrition is not being seriously considered), adverse effects can occur, whether it's related to excessive gastric residuals or micro/macroaspiration or otherwise. This approach results in underfeeding the patient, with all of its attendant adverse effects. There are studies that look at the average amount of calories that are received by patients on enteral nutrition, and it's about 60% of their prescribed calories. So once you decide in that early setting that you're going to limit yourself to enteral and not use what I would term combined modality nutrition by adding small appropriate amounts of parenteral nutrition, that patient is destined to be underfed.

In another example, there are patients with cardiac cachexia and splanchnic hypoperfusion who we anticipate will not have fully functional gastrointestinal tracts. Our approach in this setting is to use parenteral nutrition in order to meet metabolic needs as much as possible; this formula will have a low-volume. Frequently we are just providing amino acids, a little dextrose, and micronutrition. Omitting lipids can lower some risk. Dextrose itself generally does not increase the risk of bacterial infection, and may actually lower it. So, giving D10 is not going to have an adverse effect from an infectious—at least bacterial—standpoint. When you change a solution from D5 saline to D5 saline amino acids and micronutrition, you're probably not introducing any increase in infectious risk. The catheter is already inserted and there is already intravenous fluid going in to match the volume. So you are able to provide nutrition parenterally and consider adding trophic semi-elemental enteral feeds.

In addition, by dampening the effect of tube feed interruptions with simultaneous parenteral nutrition, you can reduce glycemic variability, which is an independent risk factor for outcome and probably played a large role in the successes of intensive insulin therapy protocols. Future studies may bear out that this approach confers net benefit: using low-risk parenteral nutrition continuously and trophic enteral feeds as tolerated.

**MacIntyre:** As the conference summarizer, can I quote you as saying that CCI patients, at least in the United States, are not treated aggressively enough in terms of metabolic support?

**Mechanick:** Yes.

**Carson:** In settings where tight insulin control is not working, it's often because of systemic personnel management issues. Similarly, one of the big faults of enteral nutrition is the constant stopping and restarting based on complex protocols and inadequate personnel.

One thing we did show in this clinical trial[1] is that with a good simple protocol you can get buy-in. That doesn't happen very often. Specifically, if you set your residuals higher, you don't need to check residuals very often. Thus, tube feeds, even at high rates, can run pretty consistently. If you can fix that problem with good protocols, how much of the problem of enteral nutrition remains in that setting?

1. National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307(8):795-803.

**Mechanick:** So, in a way, you support the use of tight glycemic control. You bring up the difference between effectiveness versus efficacy. Proof of concept studies in a controlled environment for efficacy and then real-life for effectiveness. When enteral nutrition is applied in a highly controlled way, where everybody is on board with nutrition protocols, clinical outcomes can improve.

Based on the institution you work at, with the industry intelligence brought to bear, you actually have options, and you should take advantage of the resources you have available for the best outcomes. So, indeed, if you have these enteral nutrition protocols in a highly controlled setting and you have data demonstrating that they work and they reduce morbidity and mortality, by all means use them.

The indirect answer for the Leuven protocol is that it was a proof of concept study[1] in a tightly controlled environment showing efficacy whereas NICE SUGAR[2] was a real world study involving many centers that may not have had expertise comparable to the Leuven group. NICE-SUGAR illustrated the pitfalls of implementing tight glycemic control without the proper infrastructure involving all personnel, resources, and administration. Enteral nutrition protocol arguments parallel this line of reasoning and require an equally controlled environment.

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345(19):1359-1367.
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