Metabolic alterations in the critically ill child

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Abstract: The metabolic response to critical illness is characterized by changes in energy metabolism and distribution of substrates and nutrients to sustain cellular function, repair, and to support the immune response and growth. Such response is regulated by simultaneous neurohormonal and inflammatory responses mediated by neurotransmitters, cytokines, hormones, and metabolic signals. The stress-mediated changes in energy expenditure (EE) are characterized by an initial phase of decreased followed by an increased EE. Inflammation triggered by cytokines is divided in several categories: interleukins, chemokines, interferons, tumor necrosis factor, and growth factors. The interleukins are divided into pro-inflammatory (responsible for cell activation, tissue damage and necrosis) and anti-inflammatory interleukins (involved in dampening and reversing the inflammatory process). The counter-regulatory response is characterized by increased concentrations of catecholamines, glucagon, and cortisol and oppose the effects of insulin. Those same elements that regulate stress, inflammation and energetic failure also induce an increase in whole-body protein synthesis, intensification of muscle protein catabolism, and a reduction in muscle protein synthesis to support a surge of amino acids (AA) released into the systemic circulation to serve as biochemical precursors, signals and structural substrates and oxidation for energy if needed. Both energetic and macronutrient processes interact and regulate themselves to establish a new homeostatic situation suited to fight infections, sustain life, and promote recovery. Due to current advances in intensive care, and modern life sustaining therapies, a prolongation of the inflammatory and catabolic state and nitrogen loss occurs, rendering the individual resistant to traditional nutrition support therapies.

Keywords: Energy metabolism; critical illness; child; catabolism; metabolic stress

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Introduction

The acute metabolic response that follows an acute illness, trauma, and surgery is characterized by increased catabolism, release of increased amounts of glucose, amino acids (AA), and fatty acids from the body’s stores (1,2). Sir David P. Cuthbertson described the fundamental aspects of this metabolic response to injury more than half-a-century ago (3,4). This response varies depending on the nature and severity of the insult, as well as, factors related to the host (i.e., age, metabolic reserve capacity, and presence of chronic conditions) (5,6). This response includes changes in energy expenditure (EE), metabolic changes mediated by proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-12, IL-18, tumor necrosis factor alfa (TNF-α), and interferon gamma (IFN-γ), hormonal responses with changes in levels of growth hormone (GH), thyroid-stimulating hormone (TSH), insulin growth factor binding proteins (IGFBP); and several metabolic reactions including increased gluconeogenesis, increased fatty acid and carbohydrate oxidation and increased loss of muscle mass...
Energy metabolism is the most important function of the body and it regulates basal metabolism, growth, and physical activity; it is controlled at the cellular level by complex reactions of the neurohormonal system and regulates the utilization of substrate. The total objective of these controlling processes is to preserve energy stability and the central nervous system (CNS) acts an essential function in achieving this balance by triggering functions at the hormonal, neural, and metabolic level (13,14).

To be able to understand the concept of energy balance is essential to examine the elements of total energy expenditure (TEE) (Figure 2). TEE has four elements: basal metabolic rate (BMR), thermogenesis, physical activity, and adaptive energy. BMR accounts for 60–70%, thermogenesis for a 10% and physical activity represents 20-30% of TEE; adaptive energy is the energy expended to adapt to environmental conditions, particularly changes in ambient temperature; throughout circumstances of stress or injury these percentages varies depending on the degree of insult, substrate intake and amount of physical activity (15-19).

Energy needs are related to age and represents up to 3 to 4 times higher per body weight for infants compared to adults (20), and are also dependent on changes on metabolic rate and body nutrients reserve. In the presence of an insult the response will be proportional to the magnitude, nature, and duration of the injury (21). Increased levels of counter-regulatory hormones will result in opposition to the actions of insulin and GH. This increased resistance to the action of insulin and GH will result in a catabolic response with breakdown of glycogen, protein, and fat to provide enough substrate to support the metabolic response (22,23).

The main reason of the augmented energy dissipation in younger children is credited to the energy expense for growth. At 6 months of age the growth velocity is maximal representing up to 6–8% of energy utilized for growth, this process slows down at the age of 12 months once the BMR is 55 kcal/kg/day, when 2% of the EE is used for growth (16). During periods of acute stress, however, somatic growth is very difficult to achieve and cannot occur. Second, critically ill children are usually sedated or treated with muscle relaxants, therefore their activity level


**Figure 2** Components of energy expenditure.

(7-12) (Figure 1).
is reduced significantly lowering their energy needs. Third, the insensible losses are significantly reduced, particularly for patients on mechanical ventilatory support. Therefore, is very important to take into consideration these changes while implementing a nutrition support plan.

The traditional concept has been that acutely ill patients present a hypermetabolic condition known as “flow phase”, preceded by a phase of reduced EE aimed to preserve energy known as “ebb phase” (17,24-32). Many studies have reported measurements of EE by indirect calorimetry in children admitted to the pediatric intensive care unit (PICU) (15,17,24-46), the aggregate result of all these measurements yields an average metabolic index [measured energy expenditure (MEE)/predicted BMR] of 1.02±0.10 (SD), indicating an average metabolic condition. Of note are the studies that reported decreased MEE in postsurgical infants and neonates using indirect calorimetry and tracer methodology indicating a hypometabolic state (47-49), therefore, the importance of adjusting the caloric intake in this population of infants and neonates to avoid overfeeding.

In summary, the metabolic response is characterized by dysregulation of the energy metabolism, therefore, is important to understand and identify these changes during the acute phase of the injury in order to implement timely and appropriate interventions to support metabolically the acutely ill patient, while avoiding underfeeding and overfeeding (16,25-27,50).

**Inflammatory response and cytokines**

The metabolic response to tissue injury is initiated by activation of the cytokine cascade. Cytokines are a group of proteins (<40 kDa) created and distributed with the objective of cell signaling (51), and after binding to specific receptors, cytokines prompt initiation, multiplication, or relocation of target cells (52). Cytokines comprises a number of groups including: interleukins, chemokines, interferons, TNF, and growth factors. During sepsis interleukins are produced and include proteins released by leukocytes and endothelial cells and include pro- and anti-inflammatory types; the interleukins with pro-inflammatory activity [IL-1β, TNF-α, IL-18, IL-12, IL-17, INF-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF)] participate in cellular activation, tissue destruction, and necrosis; the interleukins with anti-inflammatory properties [IL-10, IL-13, IL-1ra, and transforming growth factor beta (TGF-β)] are responsible for dampening and reversing the inflammatory process (52-56).

The role of cytokines including TNF-α, IL-1β, IL-6, IL-8 as important mediators of infection and tissue injury, and INF-γ as metabolic mediator have been identified in many experimental studies. In subjects with sepsis who died, IL-1β levels were higher compared to subjects that survived, implying a link between elevated levels of IL-1β and outcome in patients with sepsis (57). Several studies have been performed to provide evidence for the role of endogenously produced TNF in the development of cachexia, muscle wasting, and decreased albumin synthesis (51,52,58). The most important supplier of IL-6 is macrophages at the tissue with elevated concentrations noted in several inflammatory conditions such as cardiovascular and autoimmune diseases, or neoplasia (52). Higher levels of IL-6 have been reported in pediatric patients with sepsis compared to subjects with systemic inflammation not associated with infection (59,60). Additionally, in children with sepsis a higher level of IL-6 is linked to more severity (61), making IL-6 a useful tool to predict outcome in sepsis. IL-8 functions include chemotaxis and neutrophil stimulation and several studies have found to be a good discriminator for survival. Wong et al. reported in two studies (62,63), higher levels of IL-8 in deceased pediatric patients with septic shock compared to subjects that survived, also found that a level of IL-8 ≤ to 220 pg/mL on admission to the intensive care unit was a good predictor of survival. Two reports in children with cancer found that a low level of IL-8 was a good predictor of a low risk of bacteremia (64), and that levels >300 pg/mL in conjunction with high C-reactive protein (CRP) in children >12 years of age were associated with worse outcome in this population (65).

**CRP and procalcitonin**

CRP was discovered in 1930 by Tillett and Francis (66) and was given this name because precipitated serum when pneumococcal cell wall C-polysaccharide was present. It is an acute-phase reactant made by hepatocytes when infection or tissue injury is present (67,68). The systemic response to tissue damage caused by an inflammatory or infectious trigger, results in the production of inflammatory cytokines such as, IL-1, IL-6, and TNF-α, these cytokines stimulate the synthesis of acute phase proteins in the liver, including CRP and procalcitonin (PCT) (69-71). Serum CRP concentrations multiplies every 8 hours and reach peak levels at 36–50 hours, with a half-life of 4–7 hours (68). The utility of CRP as a tool to make diagnosis has shown to have limitations.
given its sensitivity and specificity to distinguish among benign vs. severe bacterial infection or the presence of a non-bacterial infection process. A systematic review evaluating CRP to diagnose bacterial infection accurately in ambulatory pediatric patients with fever, reported a sensitivity of 77% and specificity of 79%; this low sensitivity value suggests that CRP cannot be used to exclude all bacterial infection (72). Additionally, it is useful to monitor response to treatment after a diagnosis of infection has been done, with serial persistent high CRP levels or higher levels after 48 hours indicate inadequate treatment (67). The more recent studies in the literature of the use of CRP as a diagnostic tool has focused on the comparison of its diagnostic accuracy with the use of PCT (68).

Procalcitonin is made by the thyroid to control serum calcium concentrations and constitutes a precursor of calcitonin and it is produced by the parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine, and thyroid C cells are the only ones that express the enzymes that produce the mature calcitonin (73). The thyroid gland produces PCT and this production occurs under normal conditions with low levels detected. Under an infection challenge the production of PCT by non-thyroidal tissue is increased significantly, suggesting that initial inflammatory stimulation from TNF-α, IL-1β and IL-6 is important (68). Multiple studies have evaluated the diagnostic use and advantage of using PCT to discriminate sepsis from systemic inflammatory response syndrome (SIRS) (74-78), and reported that children with established infection had elevated values of PCT compared to children without infection (SIRS only) (78), serum PCT concentration was significantly elevated in children with sepsis compared to children without infection with SIRS after cardiopulmonary bypass, (74), and in a cohort of children admitted to the PICU, PCT was better than CRP in discriminating subjects with SIRS and sepsis with PCT elevated concentrations associated with higher severity of illness (77). The level of evidence published to date in children with infection and sepsis, preclude the routine use of PCT as a biomarker in clinical practice, as a prognostic tool and risk stratification, or to help with the decision of antibiotic treatment duration (56).

**Hormonal response**

The stress responses to injury, trauma or sepsis are mediated by a number of different hormones, protein messengers, and the development of a complex system of neural injury-induced stimuli that triggers the CNS, resulting in alterations at the hypothalamic-anterior pituitary axes, these include the adrenal gland (increased cortisol secretion), the somatotrophic (increased GH secretion), the thyrotrophic [decreased triiodothyronine (T3) and increased reverse T3 (rT3) secretion], and the gonado-/lactotrophic (decreased testosterone, increased prolactin) axes (79,80). In addition, the CNS also acts through the peripheral sympathetic nervous system to increase catecholamine secretion.

After an insult, a condition of increased resistance to the actions of the GH at the peripheral tissues is developed (9,81), this response is in part a result of the secreted cytokines. The increase in circulating amounts of GH (82) is heralded by a reduction in concentrations of GH-binding protein, indicating a reduction on the expression of the GH receptor at the level of peripheral tissues (83,84). The reduction in negative feedback inhibition explains the ample availability of GH during the initial stages of the stress response; this answer of the GH axis is instrumental in the fight for existence, where indirect insulin-like growth factor-1 (IGF-1) mediated somatotrophic effects of GH are attenuated, resulting in increased levels in the circulation of glucose and fatty acids (80). The decreased level of somatotropism, because of a lack of pulsatile GH secretion might add to the etiology of the wasting syndrome that distinguishes by a protracted course of a severe condition (79,80,85).

Shortly after the onset of severe stress there is a rapid decline of circulating levels of T3 with a concomitant increase in rT3 as a result of disrupted peripheral conversion of T4 (86,87). The instant reduction in levels of T3 might be seen as an answer to preserve energy while the substrate intake is markedly reduced (80). The persistence of low T3 after normalization of TSH levels is known as the low euthyroid syndrome. The reduction in T3 levels throughout the initial period following the insult is a reflection of the severity of the disease process (88) and this has been shown in clinical studies where a low T3 is associated with increased mortality (79,89,90).

Cortisol levels increase during the acute phase of the response to injury as a result of the increased release of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH), this is explained either by a direct mechanism or inhibition of the negative feedback by cortisol (91,92). The majority of the suppressive effects of cortisol on immune and inflammatory reactions appear to be a consequence of the modulation of production or activity of cytokines (i.e., IL-1, IL-2, IL-3, IL-6, interferon-γ,
TNF-α), chemokines, eicosanoids, complement activation, and other inflammatory mediators (i.e., bradykinin, histamine, macrophage migration inhibitory factor) (93). The most necessary and dynamic hypercortisolism induced by stress in critically ill patients results in energy provision by shifting carbohydrate, fat, and protein metabolism, suppress inflammation, and boost hemodynamics by augmented sensitization of the vasopressor response to catecholamines (80,93,94). Plausible disadvantages of prolonged hypercortisolism include impaired wound healing and myopathy, complications often seen during lengthy course of critical illness (79,80,90,94).

### Carbohydrate and lipid metabolism

During conditions of stress, hyperglycemia is a consequence of a mixture of enhanced gluconeogenesis and enhanced insulin resistance resulting in decreased glucose uptake by the cells (95) (Figure 1). These two mechanisms are potentially mediated by increases in counter regulatory hormones and proinflammatory cytokines and potentially these cytokines prevent insulin to be secreted by the pancreas via activation of α adrenergic receptors (96-98). Increased concentrations of counterregulatory hormones and proinflammatory cytokines participate in the regulation of glycogenolysis and gluconeogenesis with resultant hyperglycemia (95), and glycogen stores are rapidly depleted with glycogenolysis resulting in limited glucose production (96). The elevated concentrations of catecholamines during this acute response to injury results in elevated glucagon levels with gluconeogenesis being maintained despite elevated levels of insulin (99). Other hormonal changes including increased GH and decreased IGF-1 concentrations enable the destruction of muscle releasing alanine to enhance gluconeogenesis (100). Acute injury is distinguished by insulin resistance either central or peripheral (101), and insulin resistance at the hepatic level being central and mediated by glucagon, epinephrine, and cortisol (99). The Insulin resistance at the muscle and fat tissue is classified as peripheral and is explained by changes in the insulin-signaling pathway regulated by inflammatory cytokines and counter regulatory hormones (101). This peripheral insulin resistance might continue for a protracted time after recovery from an acute injury, as described in pediatric patients (102). Several studies have reported defects in beta-cell function of the pancreas with reduction in its ability to produce insulin in critically ill children (103,104).

The fat tissue represents the main supplier of fuel and it is depot as triacylglycerides and the breakdown or lipolysis produces non-esterified free fatty acids (FFA) (105). Lipolysis at the extracellular and intracellular space is regulated by lipoprotein and hormone-sensitive lipase (HSL). During conditions of inflammation there is a significant increase in serum levels of triacylglycerides and FFA and decrease in high-density lipoprotein concentration (106). Additionally, increased levels of cytokines and catecholamines induce blockage of lipoprotein lipase and reduced extracellular lipolysis, simultaneously, upregulation of HSL results in lipolysis at the fat tissue (105). An increased triacylglycerides synthesis results in reduced clearance of triglycerides, resulting in hepatic steatosis (107), and storage of triacylglycerides and FFA at the muscle (108,109), heart (110), and kidney (111), this is the result of a disrupted uptake FFA and its oxidation. No reported definite evidence that an alteration of the FFA oxidation is present at the mitochondrial and peroxisomal level in the acutely ill patient, but in subjects with type 2 diabetes and metabolic syndrome, these alterations modify the insulin signaling and enhances insulin resistance (112,113). Hypertriglyceridemia is an important concern because of the altered endothelial function, lipotoxicity, and increased inflammation and often lipid infusion during acute injury conditions worsens hypertriglyceridemia (105).

### AA and protein and metabolism in the critically ill

The complex interrelation of protein metabolism and metabolic partitioning during critically illness across the human lifespan emphasizes the need to individualize protein support therapy towards achievement of proteostasis (protein metabolic homeostasis) and organ support rather than simply balancing nitrogen expenditure (114-116). To sustain tissue integrity and organ function in healthy conditions, body protein is continuously degraded and resynthesized in all tissues and cells, a process known as protein turnover. Tissue proteins in different organs are constituted by AA, which normally can be either incorporated into tissue protein or undergo oxidation for energy production when energy intake is inadequate to satisfy the metabolic demands. Normally, tissue protein breakdown releases AA to the peripheral circulation, and those circulating AA may be reutilized for accretion of...
tissue protein or may perform intracellular or physiologic functions. Adult individuals are less efficient than children and neonates to convert dietary protein into net accretion and maintenance of body protein, but youngsters also require additional protein per unit of mass to include fractional needs required to sustain growth in their maintenance protein and AA requirements (115).

Skeletal muscle mass accounts for a major component of the lean body mass (LBM) as the largest protein reserve in the body. During illness, muscle and LBM correlates with severity of illness, systemic inflammation, impairment of the respiratory function and clinical outcomes in both pediatric and adult patients (117-119). Other components of the body protein reserve include circulating proteins, such as visceral proteins, acute phase reactants, hemoglobin, leucocytes, and immunoglobulins. In normal conditions, the balance between protein and AA intake, protein turnover, and nitrogen loss is aimed to maintain LBM, sustain protein compartments and homeostasis, and, in the case of children and neonates, also for lean mass growth (120). In critically ill states, pre-albumin and retinol-binding protein are more accurate to evaluate the response of the de novo plasma protein pool to dietary protein intake because of their shorter half-life, when compared to circulating proteins with a longer half-life, such as albumin (121,122).

For infants and pediatrics patients, rapid growth occurs because of efficient protein accretion of skeletal muscle mass, mediated in large part by very high protein synthesis rates in skeletal muscle and extreme sensitivity to anabolic stimulation triggered by post prandial elevation of circulating insulin and AA. Such robust post prandial response to insulin and AA stimulation in the young does not affect muscle protein degradation and it declines as the young individual becomes an adult (123-126). Therefore, normal infants and children have a more efficient use of dietary protein and AA released from endogenous proteins breakdown to conserve and grow LBM.

Critical illness induces loss and catabolism of body protein by the presence of starvation, immobility, stress, and inflammation. With current advances in intensive care and life sustaining support with extracorporeal therapies, dialysis, mechanical ventilation, medications (such as steroids, sedatives, and immunosuppressors) and the presence of organ dysfunction can cause prolongation of the inflammatory and catabolic state and add to the promotion of nitrogen loss. Such prolongation of the catabolic state creates a chronic cumulative nitrogen deficit (127).

**Nitrogen shuttle and metabolic partitioning**

During critical illness, in contrast to normal states, injury and inflammation induce protein breakdown release AA and nitrogen to the systemic circulation to provide substrate for whole body protein metabolism (128-130) (Figure 3A,B). Such metabolic response is not reversed by provision of exogenous protein as is innately driven and regulated by stress hormones, neural mediators, and cytokines. Systemic inflammation enhances protein synthesis in the liver and immune cells displaying as increased whole body protein synthesis rates. Circulating plasma AA released from body protein are preferentially used for gluconeogenesis, oxidation to produce energy, as substrate for immune cells and enterocyte metabolism, and to supply nitrogen to the liver for synthesis of acute phase reactants. Therefore, circulating plasma AA concentrations are extracted from the systemic circulation and thus achieve lower levels in patients with critical illness when compared to healthy subjects (128,130). Intestinal epithelial breakdown and a decrease in visceral protein synthesis (i.e., albumin, and pre-albumin) ensues when protein or AA are not provided in the enteral lumen for its absorption and release to the splanchnic bed (131,132). In healthy conditions, portal rather than arterial AA is preferentially used for hepatic protein synthesis of visceral protein after enteral feeding (132). Protein metabolic partitioning occurs based on specific organ needs, as different organ systems may require and uptake specific AA or when a particular AA may serve as a precursor or as a physiologic signal during critical illness (115). Thirty to fifty percent of essential AA in the diet may be catabolized by the small intestine in first-pass metabolism for enteral utilization by the enterocyte and splanchnic extraction (133,134).

As opposed to the increase in whole body protein synthesis during systemic inflammatory states, in skeletal muscle protein synthesis decreases and protein degradation increases, to decrease uptake and utilization of AA by muscle tissue and to release and shuttle AA and nitrogen to the immune cells and visceral tissues (135,136). This preference on protein degradation over protein synthesis in skeletal muscle leads to muscle atrophy and loss of LBM, and it is also associated with growth failure in children (137,138). In this regard, critically ill children have a higher protein turnover than adults, due to relatively amplified baseline higher whole-body protein synthesis and breakdown, limiting loss of LBM by their protective robust
baseline anabolic rates (135,139). Critically ill adults can achieve maximal rate of protein loss in the first 10 days, and loose more than 14% of total body protein over 3 weeks (140,141).

From studying fast or slow proteins in animal models and humans, it appears that is the rapid increase and variation in the plasma AA concentrations what leads to protein synthesis in muscle, not the absolute AA concentrations. In neonatal animal studies, intermittent boluses of protein have improved feeding efficiency, by inducing a greater stimulatory effect on skeletal muscle protein synthesis than continuous enteral feedings (126,142,143).

**Intracellular protein turnover in critical illness**

In skeletal muscle and in most organs, cellular protein mass or function are maintained by regulation of the protein synthesis and degradation balance (Figure 4). Protein synthesis in all organs occurs by triggering of a signaling pathway that stimulates translation of mRNA into protein and it can be regulated differently in different organs during critical illness. In this regard, systemic inflammation increases hepatic protein synthesis by activating the translational machinery while simultaneously impairing the efficiency of translation of mRNA into protein in muscle (144,145). Protein degradation in skeletal muscle is regulated by molecular signals involved in translation (146). Protein kinase B (PKB, also known as Akt) an insulin signaling protein, appears to link translation and protein degradation signal activation. Translation comprises activation of the mammalian target of rapamycin (mTOR) through PKB and intracellular AA. Intracellular AA also activates translation initiation via stimulation of mRNA binding to the 43S ribosomal complex; and through eIF2B, which stimulates the binding of the initiator methionyl-tRNA (met-tRNAi) to form the 43S pre-initiation complex; and dephosphorylation of the eukaryotic elongation factor 2 (eEF2) for peptide chain elongation (144,147). Systemic circulating AA require active transmembrane transport to become intracellular. PKB activation also inhibits Caspase-3 activity and restrains activation of the FoxO group of proteins. Proteases such as caspase-3 facilitate intact muscle fiber decomposition to release monomeric contractile proteins, such as actin and myosin, for further disintegration into AA by the ubiquitin-proteasome system (148). PKB and mTOR inhibition increase E3 ubiquitin ligase...

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**Figure 3** Compartmental model of whole-body protein kinetics. Diagram of the compartmental model representing whole body protein kinetics in normal conditions (A), and during fasting in the presence of critical illness and inflammation (B). Arrows towards the Plasma free amino acid (AA) pool compartment represent pathways towards catabolism and release of AA to the systemic circulation, while arrows towards the organ compartments indicate AA intake and tissue attrition. Circulating AA in the free AA pool may undergo oxidation for energy production and nitrogen waste products. Muscle protein turnover is high at baseline and their anabolic drive towards synthesis is very sensitive to anabolic stimulation in young animals. This response dampens as the organism matures, and muscle protein breakdown may not be worsened by a catabolic insult with maturity.
expression of muscle atrophy F-box (MAFbx, atrogin1) and muscle RING finger 1 (MuRF1), which have been associated with activation of the ubiquitin-proteosomal system (149,150). High protein synthesis rates in young animals are due to an enhanced translational process that declines as the animal matures (125,151). In contrast, animal studies suggest that the more intense activation of degradation signaling at baseline in skeletal muscle of young animals cannot be enhanced by inflammation, and that catabolic signal activation in skeletal manifests its severity as maturation advances (150). Autophagy appears to be an innate process that is activated by inflammation and antagonized by the presence of intracellular AA, which can antagonize autophagy signal activation (152). Moreover, protein synthesis and degradation in skeletal muscle can be regulated by the presence or absence of fiber stretch, and immobility leads to enhanced catabolic processes and decreased protein synthesis (153).

Alteration in energy metabolism during systemic inflammatory states leads to decreased translation and enhanced degradation signal activation in skeletal muscle. Inflammation may cause mitochondrial dysfunction and energy failure causing enhanced catabolic signals and decreased protein synthesis. 5’-AMP-activated protein kinase (AMPK), an intracellular energy sensor, is activated in the presence of energy starvation, inhibits mTOR and protein synthesis signal activation and activates the ubiquitin-proteosomal system (149,150,154). In neonatal animals, insulin has shown to antagonize AMPK activation and thus, appears to stimulate protein synthesis and decrease muscle protein degradation signal activation in skeletal muscle during inflammation, suggesting that insulin

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**Figure 4** Molecular regulation of protein synthesis and degradation in skeletal muscle. Representation of the signal activation sequence that leads to protein balance in tissues, cells and organs. In muscle, protein synthesis occurs when amino acids, insulin and contractility promote mRNA translation into protein. The regulation of protein degradation involves myofibrillar degradation by the ubiquitin-proteasome system and autophagy. AMPK, an intracellular energy sensor, modulates the balance between the activation of signaling pathways for protein synthesis and degradation in the presence of inflammation and stress. AA degraded from muscle are either released into the circulating AA pool, or are reutilized by skeletal muscle through translation.
resistance plays a role in skeletal muscle catabolism during critical illness (136,154).

**Protein catabolism and anabolic resistance**

Critical illness is a rapidly changing physiologic state, in which protein requirements, utilization and balance is evolving in accordance to the progression of the acute physiologic alterations. Critical illness may induce a catabolic response and a loss of LBM that may be unresponsive to exogenous nutrient support, in contrast to simple starvation (137). During critical illness, the effects of the autonomic stress response, insulin resistance, cortisol, cytokines, and the dysfunction of anabolic hormones may decrease the expected response to adequate protein provision. Both injury and inflammation lessen the response to anabolic hormones and nutrients that enhance protein deposition in skeletal muscle and maintenance of the LBM (141,144).

To preserve LBM, circulating insulin and its response are crucial for skeletal muscle protein deposition, as they stimulate protein synthesis, inhibit muscle protein degradation, and improves energy homeostasis in skeletal muscle (142,154). In this regard, insulin continues to stimulate skeletal muscle protein synthesis and inhibits muscle protein degradation during critical illness but does not attenuate whole body proteolysis when provided at higher than physiological concentrations (155-158), possibly due to the antagonism of circulating cytokines (105,159). As we explained previously, assessment of the response of protein metabolism to insulin at the whole-body level may not reflect the favorable effects of insulin in skeletal muscle during critical illness, since insulin does not affect the elevated protein synthesis rates in liver during systemic inflammation (160). Thus, due to such metabolic partitioning during critical illness, the advantageous effects of insulin on whole body protein metabolism are permissive for protein synthesis and suppressive for protein breakdown only if adequate AA are provided (105,136,157). In addition, insulin has been reported to have intrinsic anti-inflammatory properties and positive effects on reestablishing glucose and energy homeostasis and stimulation of protein anabolism in skeletal muscle (157,161-163).

In pediatric critical illness other important mediators of the stress response such as corticosteroids cause insulin resistance, hyperglycemia, net release of glutamine from muscle, and decrease in translation initiation and enhancement of protein degradation in muscle (130,164). While the epinephrine and norepinephrine are usually associated with catabolic processes on energy metabolic rate, they may have an anabolic effect on skeletal muscle protein metabolism (165). Critical illness is associated with transitory reduced levels of IGF-1, acquired GH resistance, and a decreased anabolic response to GH (141).

Branched-chain AA (leucine, isoleucine, valine), threonine, and lysine supply close to the 75% of the body's nitrogen requirement (166). Even though certain AA may directly exert physiologic or cellular effects, AA imbalances may also be negative for metabolic homeostasis, and during critical illness they may become conditionally essential. That is because all 20 protein AA and their metabolites are required for normal cell physiology and function, and their single deficiency or oversupply may blunt their intrinsic beneficial effects (167). AA are intrinsically anabolic and can stimulate a marked rise in muscle protein synthesis independent of insulin stimulation. AA requirements are also influenced by age because of increased requirements in the presence of active growth in the young individual (157). In critical illness, Alanine, Glutamine, Glycine, and Aspartic acid can act as gluconeogenic substrates, shuttling nitrogen from peripheral skeletal muscle to the circulating AA pool. Glutamine is a major constituent in muscle protein, shuttling about one-third of all AA nitrogen and serves as fuel for enterocytes and cellular immune response (168). Arginine, and its precursor citrulline, are precursors of nitric oxide, creatine, agmatine and other polyamines, and modulates protein anabolism (133,167,169). Parenteral BCAA have been used to improved outcomes in critical illness without success (128). Leucine, and its metabolite beta-hydroxy-beta-methylbutyrate, have a direct anabolic effect in skeletal muscle, and have been used to stimulate nitrogen maintenance (152,170,171).

The hypercatabolic state of injury or sepsis has been characterized a marked negative nitrogen balance (25,27,50,136,172). Nitrogen excretion is linked to the metabolic expenditure because it is affected by severity of illness. Whole body nitrogen utilization is affected by energetic deficits, and protein can also be oxidized for energy in catabolic states (25,27). During intensive care support during critical illness, nitrogen can be lost in urine, stool, skin, and in extracorporeal elements such as dialysate, extracorporeal circuits and thoracic or abdominal drainage (173-176). Therefore, even when provided with the appropriate estimated requirements, the critically ill may lose more protein than that able to assimilate (173). Although aiming for a positive protein balance has been
used as a surrogate measure of LBM preservation, it does not assess protein or AA utilization, quality of intake or protein reserves or metabolic partitioning. Moreover, sufficient amounts of energy are needed to efficiently utilize the supplemented protein. When protein and energy are supplied during critical illness, whole body protein synthesis rates are increased without affecting protein breakdown. Therefore, improvement in protein balance at the expense of higher protein synthesis may occur despite resultant ongoing losses of body protein and attaining protein balance may not prevent loss of LBM or skeletal muscle mass (27,173,177).

Even when faced with a critical illness, infants and children contrast from adults in their requirement for a continuous supply of substrate and energy to maintain growth and their protein needs. Acceptable quantities of energy are needed to efficiently use the supplemented protein, since whole body nitrogen utilization is affected by energetic deficits, and protein is catabolized to loss and oxidized for energy in catabolic conditions (25). It is recommended to adjust the normal caloric partitioning (50–60% of calories from carbohydrates, 25–35% from protein, and 10–25% from fat) to adjust to the increased protein needs to prevent AA to be used for energy production during critical illness. The calculation of calorie-to-nitrogen ratio, whether total or non-protein calories, supports the concept of providing adequate caloric intake when high protein is provided (178). Traditionally, and based on expert opinion, the recommended calorie-to-nitrogen ratio requirement has been suggested around 130–150 kcal/gram of nitrogen (1 gram of protein =6.25 grams of nitrogen) during critical illness in adults. In contrast, an energy to nitrogen (E/N) expenditure ratio of 382:1 kcal/gram of nitrogen has been described in healthy active young men and was proposed to help design the adequate caloric partitioning for enteral nutrition or parenteral nutrition support (173). In that report, the E/N ratio decreases continuously with increasing protein loss and is not a constant value (173). This evidence indicates the need for studies that specifically match intake to expenditures in critically ill individuals across the lifespan to encompass for the large variations in EE, protein loss, and E/N ratios in diverse patient populations.

Proteostasis in the critically ill child implies understanding protein metabolism and adaptation to stress (115). Studies on protein metabolism discovered that humans adapt to prolonged low protein intake and maintain of health and LBM (179) by means of metabolic adaptation and plasticity, metabolomics and epigenetics (167,180). During conditions of protein starvation, cells respond to the stress of AA deprivation through sensing the AA deficiency, leading to modulation of global protein synthesis to save EE through translation reprogramming to maintain metabolic homeostasis (180). Adequate understanding of energy and macronutrient sustenance to the metabolic adaptation to prolonged survival in intensive care when supporting critical illness will allow improved survival and recovery, and in children, restoration of growth potential.

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**Footnote**

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