Malnutrition in the acutely ill patient: is it more than just protein and energy?

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Abstract

Malnutrition has traditionally been thought to involve deficiencies in protein and energy (macronutrients); however, we know that specific key nutrients, when deficient. can also lead to significant morbidity and mortality. Large studies performed with replacement of single nutrients, such as zinc, in malnourished populations in Africa and other developing countries has led to reductions in respiratory infections and diarrhoeal diseases. In this regard, It is being increasingly that acutely ill hospitalized patients may not only be malnourished from a macronutrient standpoint, but that such patients may also be deficient in a number of key functional pharmaconutrients. This new knowledge creates a new era in nutritional support, where nutritional therapy is presenting the surgical and critical care community with a "unique opportunity" to improve patient outcomes with a safe, relatively inexpensive and effective intervention. Our vision for the future of nutritional pharmacology in surgery and critical care is one where there will be initiation of early (< 24-48 hours post-surgery or ICU admission) nutrient delivery, preferentially via the enteral route. This should be supplemented by parenteral nutrition in "at risk" patients, when adequate energy cannot be provided enterally. Pharmaconutrients to target therapy to specific disease states in such should be administered as separate components, in a manner similar to that of administering an antibiotic or drug.

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Introduction

Malnutrition is common in acutely ill patients, occurring in 30-50% of hospitalized patients.[1-3] This prevalence may be higher in critically ill patients. Hospital malnutrition has been associated with an increased risk of complications, particularly in surgical patient.[3,4] Malnutrition in hospitalized patients also increases hospital costs[5] and is associated with increased long-term mortality.[6] Unfortunately, patients' nutritional status often becomes significantly more compromised during their ICU stay, due to a number of factors, some intrinsic to the patient and some iatrogenic. Most troubling is data showing that more than half of all ICU patients worldwide are significantly underfed based on the energy they are prescribed to receive for the first two weeks of ICU care.[7] In addition, to nutrition's probable key role in survival in the ICU setting following an acute illness/injury, significant mortality occurs after critically ill patients are discharged from hospital. More than 50% of the 6-month mortality following severe sepsis occurs after the patient has been discharged from the ICU.[8] Many of these deaths are believed to occur indirectly as a result of catabolism, loss of lean body mass, lack of therapeutic physical activity, and ultimately weakness and inability to walk.[9,10] These patients often go to rehabilitation centers or go home only to die of pulmonary embolus or pneumonia because they are unable to stand, get out of bed, or perform activities of daily life. Although these patients are seen as a "success" because they survived their acute illness and were discharged from the ICU, sadly, many of these patients ultimately die or have severely limited qualities of life. Thus, the aim of nutritional support should not only involve providing care for the acute phase of illness with vasopressors, resuscitation, ventilation, and antibiotics to enhance survival, but should also aim to, apart from minimizing the mandatory catabolism that occurs during the acute phase, manage the convalescent phase of severe illness when the key intervention becomes nutrition, anabolism, and rehabilitation. Finally, new data has indicate that malnutrition may not be limited to the traditionally believed protein and energy (macronutrient) deficits as recent evidence supports the concept that adequate nutrition may also hinge on our ability to provide key pharmacologically acting nutrients[11] (such as glutamine and arginine). This data has helped spawn the new field of "nutritional pharmacology". This review will cover the latest thinking in the field of malnutrition in the acutely ill patient.

Pathophysiology and teleology of malnutrition and nutrition therapy in acute illness

The last 50 years of medicine and critical care have brought great advances in the treatment of disease with novel pharmacologic agents. Largely ignored has been the vital role of basic nutrients and

energy in the treatment of critical illness and injury. This poor critical care nutrition delivery has resulted from years of poorly designed or non-generalizable trials in the fundamental feeding and nutritional support of our patients. Further, there has been a lack of laboratory-based exploration into the mechanistic science underlying the risks and benefits of nutrition and nutrient administration following injury and illness.

Traditionally, the lack of focus on nutrition as a vital supportive therapy in the critical care setting has been due to the observation that, in nature, acute illness reduces food intake by inducing anorexia, loss of appetite, or simply not permitting the organism to forage for food. At its discovery, tumor necrosis factor-alpha (TNF-α) was known as cachexin. This and other cytokines released in the first few hours following stress and injury induces anorexia and catabolism. The early systemic inflammatory response (SIRS) pathway has been preserved through many years of evolution. Thus, the body has previously utilized anorexia and catabolism in the face of stress and injury as a key survival mechanism. However, it must be realized that until the last 150 years if the proverbial "saber-tooth" tiger attacked, one had perhaps 48 hours to recover before one died. Even if one survived your initial injury, one was often left behind by one's tribe as a liability, for one could not gather food, reproduce, and they likely had to carry the injured who was less than ideal when other "tigers" were lurking. Survival from acute injury involved achieving hemostasis and preventing rapid, overwhelming infection. Thus, eating and anabolism were not part of this primal fight for survival. Our understanding and management of this survival mechanism has changed dramatically since the evolution of emergency medicine, surgery, and critical care. In today's environment severely ill and injured individuals are supported through massive injurious insults, when such are compatible with recovery. Thus, while we have learned to accept that lean body mass catabolism is mandatory, long-term survival mandates that we minimize lean body loss by early energy/substrate delivery in the acute phase. Aggressive feeding and perhaps pro-anabolic therapy should also follow such support in the recovery or convalescent phase. Indeed, adequate nutrition may hinge not only on how much energy we provide, but also on the ability to provide key pharmacologically acting nutrients.[11] For example, rapid mobilization of amino acids stored in muscle is a vital mechanism for survival following acute illness or injury. These amino acids (such as arginine and glutamine) are utilized as obligate nutrient sources for the immune system and the gut. Recent data indicates that these amino acids also serve as a key stress signals that initiate activation of fundamental cell protective pathways following an insult.[11] For various teleological reasons, the body becomes rapidly depleted of these substrates and their supplementation may be fundamental for optimal recovery. This data has helped spawn the new field of "nutritional pharmacology".

Epidemiology and role in outcome of ICU malnutrition

A recent review of the world literature found that in 20 studies since 1990 the mean malnutrition rate in the hospital was 41.7%.[12] Hospital malnutrition has been associated with an increased risk of complications, particularly in surgical patients.[3,4] Malnutrition in hospitalized patients also increases hospital costs[5] and is associated with increased long-term mortality.[6] Unfortunately, patients' nutritional status often becomes significantly more compromised during their ICU stay. This malnutrition is due to a number of factors, some intrinsic to the patient and some iatrogenic.

The key to providing successful nutrition therapy appears to begin with the initiation of enteral or oral feeding within 24-48 hours of admission to the ICU, and appropriate resuscitation. A recent observational cohort study of nutrition practices in 167 ICUs across 21 countries was conducted to evaluate worldwide nutrition practices in 2 772 patients. Despite multiple international guidelines recommending early initiation of enteral nutrition in the ICU, success was achieved in terms of delivering approximately only 50% of the prescribed daily energy for the entire first two weeks of ICU admission. In addition in some major developed countries, like the U.S, it takes over 60 hours to initiate any enteral feeding at all.[7] By comparison, the administration of only 500 mg of the prescribed 1 gram of vancomycin to be given daily to a patient dying of MRSA sepsis would never be tolerated. Yet, inadequate delivery of energy and nutrients is a daily occurrence in every ICU in the world (except, perhaps ironically, in Burn Intensive Care Units, where often the most severely injured patients in the hospital reside).

As with any pharmacologic therapy, it appears that not all ICU patients are created equal when it comes to their need for energy and protein. In the same cohort study,[7] body mass index (BMI, kg/m^2) was utilized as a surrogate marker of nutritional status prior to ICU admission.[13] Regression models were developed to explore the relationship between the nutrition support received during hopsitalisation and the 60-day mortality in relation to BMI status. Overall, study patients received a mean of 1 034 kcal/day and 47 g protein/day for the first 14 days. There was a significant inverse linear relationship between the odds of mortality and total daily energy received.[13] An increase of 1 000 calories per day was associated with an overall reduction in mortality (odds ratio for 60-day mortality 0.76, 95% confidence intervals [CI] 0.61-0.95, p=0.014). This beneficial treatment effect of increased energy provision on mortality was observed in patients with a BMI < 25 and ≥ 35 with no benefit for patients in the BMI 25 to < 35 group. Mortality was also reduced for every additional 30 g of protein per day given to these patients. This mortality benefit held true after adjusting for the severity of illness and other related patient factors. Thus, like with all pharmacologic interventions, some patients may benefit a great deal more from the provision of energy early in their ICU stay, while others may not benefit at all. This is a key issue, when considering the use of early parenteral nutrition (PN) whether as a primary energy source or more appropriately as a supplement to the often inadequate enteral feeding support. From this data, it might be inferred that early use of PN might be of benefit in patients with a BMI of < 25 or > 35, whereas a patient with a BMI of 25-35 may not benefit from early PN use, and in fact may only be

exposed to the inherent risks that PN can carry. A number of large randomized controlled trials (RCTs) are now planned or underway to investigate this relationship further.

Does nutrition play a role in long-term outcome and quality of life?

In addition to nutrition's probable key role in survival in the ICU setting following an acute illness/injury, significant mortality occurs after critically ill patients are discharged from the hospital. More than 50% of the six-month mortality following severe sepsis occurs after the patient has been discharged from the ICU.[8] Recent data reveal that one third of patients discharged following community acquired pneumonia are dead at one year.[9] It should therefore always be born in mind that nutritional support is necessary in the convalescent phase of severe illness when the key intervention becomes nutrition, anabolism, and rehabilitation.

Nutritional management of the ICU and acutely ill ICU patient

Key considerations in the nutritional therapy of ICU patient include: (1) route of feeding: enteral versus parenteral, (2) when to feed: begin within 24-48 hours of ICU admission preferred (early enteral feeding), and (3) what to feed: a standard enteral formula or one with targeted functional pharmaconutrients.

Practice guidelines in Europe, Canada, and the US endorse enteral feeding for patients who are critically ill and haemodynamically stable.[14-16] Enteral nutrition is preferred over parenteral nutrition (PN) for most ICU patients—an evidence-based practice supported by a number of clinical trials involving a variety of critically ill patient populations, including those with trauma, burns, head injury, major surgery, and acute pancreatitis.[16,17] For ICU patients who are haemodynamically stable and have a functioning gastrointestinal tract (GI) tract, early enteral feeding (within 24-48 hours of arrival in the ICU) has become a recommended standard of care.[14-16] Experts identify these early hours as a window of opportunity to provide nutrition that maintains gut barrier function and support immune responses.[14,16]

Patients with extreme haemodynamic instability (rising plasma/blood/serum lactate concentrations or escalating requirements for vasopressors) are generally not considered as candidates for enteral feeding. However, early findings suggest the use of early enteral feeding in other vasopressor-dependent patients may be possible. In one study, vasopressor-dependent patients who were given enteral feeding within the first 48 hours had a significant survival advantage compared to those whose feeding was delayed; in fact, the sickest patients (on multiple vasopressors) experienced the greatest benefit.[18] It should be noted, however, that this finding is based on an observational study only and confirmatory prospective from controlled studies is warranted.

PN is necessary in critically ill patients who do not have an intact GI tract or who cannot meet goal energy targets via the enteral route, but current guidelines do not agree on when to initiate PN.[19] For patients who are intolerant or have other contraindications to enteral feeding, European guidelines recommend starting PN within 24-48 hours, if the patient is not expected to be on oral nutrition within 3 days.[20] US guidelines hesitate to recommend PN on admission to the ICU; standard care (intravenous fluids) is recommended first, with PN reserved and initiated only after seven days in well-nourished patient.[16] Both the ESPEN and ASPEN guidelines recommend early PN use (within 24 hours of ICU admission) in patients who are malnourished.[16,20] Canadian guidelines state that PN should not be used in patients with an intact GI tract.[21]

When enteral feeding alone is inadequate, some experts suggest the combined use of PN and enteral nutrition to meet energy and protein targets.[13,19,22,23] Combination regimens are justified by observations that actual enteral intake typically meets only half of prescribed energy in ICU patients.[24-27] For patients who are expected to be mechanically ventilated more than 72 hours and have body mass index (BMI) scores < 25 or ≥ 35, each additional 1 000 kcal/day or 30 g protein/day was reported to be associated with reduced mortality.[13] However, clinical evidence for combination feeding remains unclear. In this regard, Casaer et al conducted a large, single center prospective, randomized trial (EPaNIC trial)[28] comparing outcomes in critically ill patients on enteral nutrition who had early versus late initiation of PN (early: < 48 hours after ICU admission, n=2 312; late: day 8 or later after ICU admission; n=2 328). Results revealed patients on late-initiation PN had a relative increase of 6% in the likelihood of being discharged alive earlier from the ICU and from the hospital (P=0.04). Those in the late-initiation group also had significantly fewer ICU infections, shorter duration of mechanical ventilation and a shorter course of renal replacement therapy. Several aspects of the study limit generalizability of the findings to all ICU populations: (1) Patients with chronic malnutrition were not included in the study. (2) Patients in the trial received a low protein delivery (median of 0.8 g/kg/day protein (after day 3) for the study period in the early PN group. This protein target was below what is recommended by most guidelines for critically ill patients (typical recommendation: 1.3-1.5 g/kg/day (ESPEN guidelines). (3) Finally, the trial examined a low mortality-risk patient group with an average ICU mortality of 6.2% (90d mortality-11.2%) and a relatively low acuity patient group with an ICU LOS of 3.5 days, and mechanical ventilation period of two days. Accounting for the aforementioned limitations, The EPaNIC trial is unquestionably a key contribution to the literature on supplemental PN use in critical care. It would thus appear that the key conclusion of the EPaNIC trial is that in low mortality risk, non-chronically malnourished patients, early aggressive energy delivery via PN does not appear to be beneficial. In contrast, the recently published, single center TICACOS trial showed that hospital and 60-day mortality was reduced ($p < 0.02$ for both time points) in a higher mortality-risk group of ICU patients receiving additional energy via enteral nutrition supplemented with PN.[29] In comparison to the EPaNIC trial, the TICACOS trial was conducted in a higher mortality-risk ICU patient group with an ICU mortality of

Table I: Summary of expert recommendations for specific pharmaconutrients in ICU/acutely ill patients[15,16,21]

Patients	Canadian CPG*	ESPEN*	ASPEN/SCCM*
General ICU	Arginine (no benefit) Glutamine (intravenous: strong benefit)	No recommendation Glutamine (intravenous: strong benefit)	Arginine (possible benefit) Glutamine (enteral: possible benefit; intravenous: strong benefit)
Elective surgery	No recommendation	Arginine (benefit)	Arginine (benefit)
Trauma	Arginine (no benefit) Glutamine (possible benefit)	Arginine (benefit) Glutamine (benefit)	Arginine (benefit) Glutamine (possible benefit)
Burns	Arginine (no benefit) Glutamine (possible benefit)	No recommendation Glutamine (benefit)	Arginine (benefit) Glutamine (possible benefit)
Sepsis	Arginine (harm)	Arginine (harm if severe sepsis; benefit if mild)	Arginine (harm if severe sepsis; benefit if mild/moderate)
ALI/ARDS	Ω-3 fatty acids and ω-6 gamma-linolenic acid (benefit)	Ω-3 fatty acids (benefit)	Ω-3 fatty acids and ω-6 gamma-linolenic acid (benefit)
Enteral feeding intolerance	Whole-protein formulas for most patients; hydrolyzed protein formula may be considered for patients with GI dysfunction such as short bowel syndrome, pancreatitis	Whole-protein formulas for most patients; hydrolyzed protein formula may be considered for GI dysfunction such as pancreatitis	Hydrolyzed protein formula may be considered for patients with GI dysfunction such as persistent diarrhea, pancreatitis

Abbreviations: Canadian Critical Care Practice Guidelines, Canadian CPG; European Society for Clinical Nutrition and Metabolism, ESPEN; American Society for Parenteral and Enteral Nutrition, ASPEN; Society of Critical Care Medicine, SCCM.

25.4% (60-day mortality 47%), ICU LOS of 12 days, and a mechanical ventilation period of 10.75 days. Thus, it is possible that in high mortality risk ICU patients supplemental PN may improve outcome. Additional trials on the use of enteral nutrition with supplemental PN have recently been completed or are underway. These forthcoming results should continue to clarify the utility of supplemental PN use in the ICU.

Expert guidelines and mechanistic explanation for pharmaconutrition in the ICU/acutely ill patient

Evidence-based nutrition guidelines for critically ill patients have been developed in North America and Europe.[15,16,21] While the guidelines agree in principle regarding pharmaconutrients, there are some differences in specific recommendations (Table I).

Immune-modulating enteral nutrients: arginine

There are a number of "conditionally essential" pharmconutrients, which become depleted during stress associated with surgery, trauma, and critical illness. These nutrients, are vital to maintenance of immune homeostasis as immune dysfunction is common in patients with nutritional deficits, particularly in patients following physical injury, such as trauma or surgical injury.[30] A key example of this nutrient-induced immune dysfunction is the arginine deficiency known to develop in patients who have experienced surgery or trauma,[30] as well as in malignancy settings.[31]

Results of recent investigations have helped elucidate how the function of the immune system is intimately linked to arginine metabolism.[31] Arginine has long been known as a biosynthetic substrate for nitric oxide (a signaling molecule for immune and other cells).[32-34] However, the improved understanding of the pathophysiology following physical injury indicated that immature cells of myeloid origin appear in circulation and in lymph tissues. These cells express arginase-1, a key enzyme in the degradation of arginine. Coupled with poor arginine intake and with an inadequate endogenous synthesis of arginine, arginase 1 expression leads to a state of conditional arginine deficiency. The latter is associated with suppression of T-lymphocyte function; the cells sunthesising arginase-1 are thus called myeloid-derived suppressor cells (MDSC). Dysfunction of T-lymphocytes after surgery or trauma is characterized by a decrease in the number of circulating CD4 cells; blunted T-cell proliferation; production of IL-2 and interferon gamma; and loss of the zeta (ζ) chain, a peptide essential in the T-cell receptor complex.[31]

Results of several clinical studies showed that repletion of arginine, along with Omega-3 (ω-3) fatty acids, helps restore T-lymphocyte numbers and function, i.e. CD4 cell counts and IL-2 production.[31,35] It also appears that dietary Ð-3 fatty acids blunt the expression of arginase 1.[36] Thus, substantial, but variable, evidence supports the concept that immune-modulating diets may exert their beneficial effects by restoring T-cell function that was impaired by MDSC-mediated arginine depletion.

The clinical outcome data (more than 30 trials and nearly 3 000 patients) support a significant treatment effect of arginine therapy (at doses delivered in immune-modulating nutritional formulas, ~ 12 g/day) following major surgery; arginine treatment reduced risk of infection (relative risk, RR = 0.58; 95% confidence interval, CI, of 0.48 to 0.69, P < 0.00001) and overall length of stay (LOS; weighted mean difference = -2.09 with 95% CI of -3.20 to -0.97, P = 0.0002) versus standard enteral nutrition[37] please clarify what the stars refer to. However, very little benefit, and perhaps harm, is observed in septic patients.[38,39] This potential harm may be caused by promotion of excessive nitric oxide production in patients with sepsis, in turn worsening SIRS and increasing risk for mortality.[40]

In summary, in the perioperative period formulations with arginine (commonly combined with ω-3 fatty acids in most trials) are given a grade A recommendation to reduce infection and shorten length of stay as compared to standard formulation. In fact, given the availble evidence from clinical trials with a consistent outcome of reduced infection, most experts would advocate arginine therapy in the peri-operative period should be standard of care in high risk surgical patients.[37] However, given that < 1% of surgical patients in the U.S. receive arginine therapy in the peri-operative period (personal communication, J. Ochoa M.D.), it is likely that a large, multi-center, definitive U.S. trial will be required to establish this practice. Trauma patients, may also benefit from supplemental arginine following injury.[32] For patients with severe sepsis, arginine-supplemented enteral formulas should be used with extreme caution[16] or avoided due to potential for harm.[15,21,40,41]This conservative approach supports the basic pharmacologic premise that with pharmaconutrients, as with traditional "drugs", "one size does not fit all" and a given pharmaconutrient will benefit one patient and have no effect or risk in another.

Anti-inflammatory nutrients: omega-3 (ω-3) fatty acids

The systemic inflammatory response syndrome (SIRS) is a common sequelae of surgical and critical illness. Patients with SIRS can evolve to the more sever conditions such as: sepsis, acute lung injury (ALI), or acute respiratory distress syndrome (ARDS). An example of a widely studied anti-inflammatory pharmaconutrient is dietary ω-3 fatty acids, which can blunt out-of-control inflammatory responses and improve outcome by modulating synthesis of pro- and anti-inflammatory mediators.[33,34,42]

Dietary intake of certain fats, such as ω-3 Fatty Acids (found commonly in fish oil), can alter the fatty acid composition in membranes of cells involved in immune inflammatory responses, i.e. neutrophils and macrophages. Certain membrane fatty acids, e.g. arachidonic acid (AA) serve as precursors to inflammatory eicosanoid and leukotriene mediators, while other fatty acids (eicosapentaenoic acid (EPA); docosohexaenoic acid (DHA); gamma linolenic acid (GLA) are metabolized to form less pro-inflammatory mediators.[33,34,42] The anti-inflammatory actions of ω-3 fatty acids EPA and DHA are thought to occur by: (1) blunting production of pro-inflammatory mediators as a result of substituting for AA in macrophage and neutrophil membranes and (2) inhibiting production of pro-inflammatory mediators from AA by competing for the metabolic enzymes cyclooxygenase and lipoxygenase. In addition, DHA and EPA are precursors of resolvins and protectins, which help resolve inflammation and reduce tissue injury.[43]

A recent review discusses the variability in outcome benefit seen in recent results of clinical trials utilizing ω-3 fatty acid therapy in critically ill patients.[44] This variability is thought to be due to use in these trials of different formulations, doses, and type of administration (continuous versus bolus).[44] However, studies examining the continuous administration of high dose (> 5 g/day) enteral ω-3 fatty acids (EPA) and borage oil (GLA) have consistently showed significant benefits in 3 clinical trials of mechanically ventilated patients with ALI/ARDS or sepsis/septic shock.[45-47] Use of this anti-inflammatory therapy significantly reduced time on ventilator, ICU and LOS, and incidence of new organ failure. Further, in a meta-analysis of the data from these three studies showed that use of an ω-3 fatty acid therapy significantly reduced the risk of 28-day mortality by 49%.[48] Results of another large meta-analysis showed that ω-3 fatty acid therapy significantly reduced by half the risk for mortality and secondary infections and significantly shortened LOS by more than 6 days in ICU patients with sepsis/ARDS.[41] All guidelines currently recommend the use of continuously administered enteral ω-3 fatty acids in ALI/ARDS patients. Additional trials are being completed studying the effects of ω-3 fatty acids in early sepsis and further phase 2 dosing trials are needed to define the ideal dose and route and type of administration in ICU patients.[44] In summary, given the latest data, ω-3 fatty acid based formulas should be Recommended to be given as continuous enteral infusion with complete enteral feeding in ARDS patients. These formulas do not appear to be efficacious in patients, when given as a single agent and/or as bolus doses.

Cell protective pharmaconutrients: glutamine

Both glutamine (GLN) and antioxidants have been found to play key roles in protecting cells against injury and patients against complications, such as infection, and mortality in the surgical, trauma, and critical care settings.[21,33] In the interest of brevity only GLN will be discussed in this review. Other reviews on antioxidants in acute care settings provide additional additional information.[33,49]

GLN rapidly becomes deficient in many hospitalized patients, including those with sepsis, trauma, surgery, or burns.[33,34,50,51] GLN is the most abundant free amino acid in the body, but stores are rapidly depleted during critical illness or injury.[34,50,52] GLN serves as a metabolic substrate for enterocytes and immune cells, supporting barrier and immune functions.[52] Recently, GLN has been proposed as a signaling molecule that is important in states of illness and injury, i.e. a messenger to turn on genes involved in cell protection and immune regulation.[53] An example of this fundamental stress signaling function is GLN's keys role in enhancing the synthesis of heat shock proteins (HSPs), which are essential to cellular recovery following injury and to protection against organ failure.[52] In fact, GLN is proving to be required for the activation of the gene(s) for HSP expression, and GLN deficiency creates a state in which the transcription factor for the HSP genes [heat shock factor-1 (HSF-1)] cannot become activated and bind the promoter (heat shock element) for the HSP genes.[54] This signal appears to be propagated via GLN's metabolism in the O-GlcNAc pathway, which is a key pathway in the cell's rapid response to stress and injury.[55] Thus, GLN appears to be required for the cell to mount an appropriate response to stress or injury.

GLN has shown the greatest clinical benefit in critically ill patients, who typically have the most severe GLN deficiency.[56] Further, GLN

deficiency on admission to the ICU is correlated with increased mortality.[57] The most recent data strongly support the use of GLN therapy to reduce mortality in patients receiving parenteral nutrition in the ICU.[21] This recommendation is supported by all available clinical nutrition guidelines worldwide.[15,16,21] Supporting data come from 4 level 1 and 13 level 2 RCTs totaling the experience of the nearly 900 patients studied; these studies reveal GLN-supplemented parental nutrition is associated with a significant reduction in overall mortality (RR 0.71 with 95% CI from 0.55 to 0.92, P = 0.008),[21] significant reductions in infection and LOS with parenteral GLN therapy.[21] A meta-analysis of all GLN RCTs (both enteral and parenteral) indicate a statistically significant reduction in mortality in ICU patients of all types (21 studies, > 1 500 patients).[21] As is true with any "drug", adequate GLN dosing is essential for clinical benefit. A parenteral GLN dose of 0.5 gr/kg/day appears to be optimal for the survival benefits seen in previous trials. Further, an enteral GLN dose greater than 0.3 g/kg/day is required for benefit; 0.5 g/kg/day (in divided portions) is likely optimal.[21] Doses less than 0.2-0.3 g/kg/day have typically not been associated with clinical benefit. While GLN supplementation is strongly recommended for the mortality reduction in patients receiving parenteral nutrition in the ICU (Grade A recommendation by all available guidelines), GLN supplemented enteral formulae are recommended (Grade B) only in burns and trauma patients.[15,16,21] Moreover, guidelines generally support the enrichment with antioxidant vitamins and trace elements in all enteral formulas.[15,16,21]

In summary, the best practice approach for the treatment and prevention of malnutrition in the acutely ill patient includes (Table II) nutritional support delivery that should be initiated early in the patient care (< 24-48 hours post-surgery or ICU admit), preferentially via the enteral route. This should be supplemented by parenteral nutrition in "at risk" patients when adequate enteral energy cannot be provided. Pharmaconutrients to target therapy to specific disease states as separate components, much like an antibiotic or drug is given, should also be considered in the appropriate setting.

The "renaissance" in our understanding of malnutrition and nutritional pharmacology is highlighted by a significant number of newly completed or ongoing RCTs (often multi-center) examining the benefits of nutrition therapy and pharmaconutrition. Further, mechanistic laboratory advances in our understanding of the role of nutrients as pharmacologic agents are now being translated into focused trials on specific nutrients. As such, it is exciting to see the application of basic clinical pharmacology, molecular biology, and clinical research principles to the better study of nutritional support in surgery and critical illness. The outcomes of these trial provide findings that afford better perspective on the questions around how to administer the right nutrients, in the right amounts, at the right time, safely.

Table II: Key management points in the prevention and treatment of malnutrition

1. A qualified ICU dietitian should perform nutrition assessment, as this has been shown to improve nutritional outcomes in the ICU.
2. Early enteral nutrition (EN) should be initiated in all critically ill patients with a functioning gut who are not expected to be taking adequate per os intake (more than 50% of needs) in 48 hours.
3. Feeding should be initiated via nasogastric tube.
4. Promotility agents (metoclopramide and/or erythromycin) should be initiated, if EN is not tolerated.
5. Gastric residuals of greater than 350-500 cc's should be considered to indicate GI intolerance of EN.
6. Small bowel feeding tubes should be placed, if nasogastric feeding with a pro-motility agent is not successful; additional measures for the prevention of aspiration should be instituted.
7. Parenteral nutrition (PN) should be initiated, if EN is not at 80% of goal for energy after 48 hours in nutritionally high-risk patients. Defined as: 1. BMI < 25 or BMI > 35; 2. Greater than 10% weight loss of usual body weight; 3. NPO more than 5 days.
8. PN should likely be initiated at 5-7 days in patients with normal pre-ICU nutritional status.
9. EN with supplemental PN does not appear to benefit non-chronically malnourished patients with low risk of ICU mortality and/or short length of ventilation (< 3 days) or short expected ICU LOS (< 5 days). However, indications of benefit are present for supplemental PN in high mortality risk, long staying ICU patients.
10. Pharmaconutrients are indicated in select populations:
    - Glutamine:
      - Strongly recommended to give in all ICU patients on PN (0.5 g/kg/day where IV glutamine is available).
      - Recommended enterally in burns and trauma patients (0.5 g/kg/day).
    - Arginine containing formulae:
      - Strongly recommended (enterally) in all pre-surgical patients having major GI, cardiac, and ENT surgery regardless of nutritional status.
      - Not recommended in sepsis or shock.
    - Fish oil:
      - Recommended to be given as continuous enteral infusion with complete enteral feeding in ARDS patients. Does not appear to be efficacious in patients when given as a single agent and/or as bolus doses.

Declaration

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