Is early starvation beneficial for the critically ill patient?

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Purpose of review
Anorexia is a preserved evolutionally response that may be beneficial during acute illness. Yet current clinical practice guidelines recommend early and targeted enteral nutritional support. However, the optimal timing of the initiation of enteral nutrition and the caloric and protein requirements of critically ill patients is controversial.

Recent findings
Starvation promotes autophagy and this may play a key role in promoting host defenses and the immune response to intracellular pathogens. Because of the perceived benefits of early enteral nutrition and the lack of clinical equipoise, randomized controlled trials comparing short-term starvation to targeted normocaloric enteral nutrition have until recently not been performed. The results of the recently reported PYTHON trial (Pancreatitis, Very Early Compared with Selective Delayed Start of Enteral Feeding) dispel the notion that short-term starvation is harmful. Furthermore, six recent randomized controlled trials that compared trophic and permissive underfeeding to normocaloric goals, failed to demonstrate any outcome benefit from the more aggressive approach. In addition, recent evidence suggests that intermittent enteral nutation may be preferable to continuous tube feeding.

Summary
Limiting nutrient intake during the first 48–72 h of acute illness may be beneficial; in those patients who are unable to resume an oral diet after this time period intermittent enteral nutrition targeting 20–25 cal/kg/day is recommended.

Keywords
anorexia, autophagy, critically ill, metabolic function, nutrition, starvation

INTRODUCTION

Nutritional support is considered an essential component of the management of critically ill patients [1▪▪], with Clinical Practice Guidelines emphasizing [2–4] early and targeted enteral nutrition. Furthermore, the caloric deficit accrued during a patient's ICU stay is widely believed to have adverse outcomes [1▪▪]. However, the optimal timing of the initiation of enteral nutrition and the caloric and protein requirements of critically ill patients is controversial. Recent randomized controlled trials (RCTs) dispel many of the widely adopted recommendations of the Clinical Practice Guidelines. This paper reviews the potential benefits of short-term starvation and the results of recent RCT that have investigated alternative feeding strategies in the critically ill.

ANOREXIA: AN IMPORTANT HOST DEFENSE MECHANISM

Exposure of the host to diverse noxious stimuli results in a stereotypic and coordinated response, referred to by Hans Selye as the 'general adaption syndrome' (or acute stress) that serves to restore homeostasis and enhance survival [5]. The acute phase response is an integrated set of physiological and behavioral reactions that are an integral part of the general adaption syndrome [6▪]. Physiological changes include fever, hyperglycemia, increased production of lactate, increased synthesis of C-reactive protein, an increase in the number of circulating white blood cells and increased slow-wave sleep. In addition, a variety of affective, cognitive, and behavioral phenomena are part of the acute phase response, including malaise, lethargy, and anorexia [6▪,7]. Proinflammatory cytokines play

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KEY POINTS

- Anorexia is a preserved evolutionary response during acute illness that may improve host survival.
- Starvation-induced autophagy is an important host defense against intracellular pathogens.
- A recent RCT dispels the notion that short-term starvation is harmful.
- Six recent RCTs that compared short-term trophic and permissive underfeeding to targeted normocaloric nutritional goals failed to demonstrate any outcome benefit from normocaloric nutrition.
- Intermittent enteral nutrition may be preferable to continuous tube feeding.

a major role in mediating the acute phase response and are believed to trigger the anorexic response to acute illness [6▪,7]. Several proinflammatory cytokines, such as IL-1, IL-2, IL-6, IL-8, IL-18, TNFα, and INFγ have been implicated in endotoxin-induced anorexia [8]. Although there is redundancy and overlap between these cytokines INFγ appears to play an important role in mediating endotoxin-induced anorexia. Activation of cyclooxygenase-2 in blood–brain barrier endothelial cells with the release of prostaglandin E_2 that then acts on serotonin neurons in the midbrain raphe are believed to play an important role in mediating anorexia [7].

Leptin, which is not considered to be a classical cytokine, has also been implicated in endotoxin-mediated anorexia. Endotoxin and proinflammatory cytokines increase the expression and production of leptin in adipose tissue. Leptin binds to specific receptors in the hypothalamus activating complex neural pathways that diminish appetite [9–11]. Leptin also interacts with the mesolimbic dopamine system, which is involved in motivation for and reward of feeding, and the nucleus of the solitary of the brainstem to contribute to satiety [12]. Endotoxin also reduces orexin expression and the activity of orexin neurons in the lateral hypothalamic area promoting anorexia [8].

The acute phase response is considered an adaptive response that is critical to host defense and survival [5,6▪]. Anorexia is considered an important element of this response. Complex and redundant pathways have evolved to ensure that the host becomes anorexic during acute illness. Folklore that dates back to the 1500s suggests that 'fasting is a great remedy for fever' [13]. Evolution does not make mistakes; therefore, anorexia during acute illness must enhance the survival of the host. However, the mechanisms whereby decreased nutrient intake is protective and promotes survival during acute illness are not entirely clear. This response would appear to be counterproductive as malnutrition results in impaired cell-mediated immunity with changes in peripheral-lymphocyte subsets (decreased CD3+, CD4+, and CD8+) and a Th1 to Th2 cytokine shift [14–16]. However, a number of diverse mechanisms may explain the protective effects of anorexia during acute illness. Humans evolved in an environment of nutrient shortage and anorexia may enhance the survival of the sickened host who may have reduced ability to hunt or gather food. Hart has suggested that decreased food motivation during illness reduces the possibility of predation while the animal is less vigilant [17]. The acute phase response is associated with a dramatic fall in serum iron concentrations [18]. Iron is an essential element required for the survival of many pathogens and iron deprivation retards bacterial growth [19]. Food restriction results in a dramatic reduction of iron in the liver and serum of a variety of organisms [20]. It has been postulated that fever and iron deprivation act synergistically to inhibit bacterial growth [21].

STARVATION-INDUCED AUTOPHAGY AND THE IMMUNE RESPONSE TO PATHOGENS

Starvation promotes autophagy and this may play a key role in promoting host defenses [22,23]. Autophagy is an evolutionary highly conserved process in virtually all eukaryotic cells [22,24]. This adaptive mechanism occurs in response to stress and promotes the survival of the cell under these conditions [22,23,25]. Autophagy involves the sequestration of regions of the cytosol within double membrane-bound compartments and delivery of the contents to the lysosomes for degradation [26,27▪]. Autophagy cannot only handle degradation of cytosolic macromolecules, but also much larger structures such as cell organelles and intracellular pathogens [26,27▪]. The most important initiator of cellular autophagy is nutrient starvation. During starvation autophagy provides a nutrient source, promoting survival. Starvation-induced autophagy is mainly regulated by target of rapamycin, a kinase that inhibits autophagy [22,24]. Nutrient starvation induces autophagy by inhibiting target of rapamycin [28]. Autophagy is a component of innate immunity and is involved in host defense elimination of pathogens [23]. Autophagy contributes to immune response against intracellular bacteria, parasites, and viruses [29]. Bacteria and viruses are vulnerable to autophagic destruction; successful pathogens have evolved strategies to circumvent autophagy [29]. Autophagy plays a role

in the degradation of both extracellular bacterial pathogens that invade the cell (e.g., group A Streptococcus) and true intracellular bacterial pathogens (e.g., Mycobacterium tuberculosis and Shigella flexneri) [30].

In a classic study, Murray and Murray [31] compared the survival of mice infected with *Listeria monocytogenes* who were force-fed to normal energy intake with infected mice who were allowed to feed *ad libitum*. In this study, survival time was decreased and mortality increased in the force-fed mice with survival being greatest in those mice who lost the most amount of weight. Subsequently, these authors prospectively studied the occurrence of infections in a large cohort of primary famine victims before and during refeeding [32]. The authors demonstrated that refeeding significantly increased the risk of infection, mostly because of intracellular pathogens. Similarly, Wing and Young [33] demonstrated that mice infected with a lethal dose of *L. monocytogenes* who had been starved for 72 h had mortality at 24 h of 5% compared with 95% mortality for fed mice. The findings of these studies may be related to the fact that starvation promotes autophagy that destroys intracellular pathogens such as *L. monocytogenes* [29].

From a teleological perspective, starvation would appear to be beneficial during the initial phase of acute illness, particularly bacterial sepsis. The selective advantage of this host defense mechanism evolved over tens of thousands of years in the absence of antibiotics and critical care medicine, which are a very recent phenomenon. The experiments described above with *L. monocytogenes* were performed in the absence of antibiotics; it is not clear that survival of the starved animals would have been better than the fed animals had both groups been treated with antibiotics. Furthermore, in the protected environment of an ICU, patients are rarely attacked by predators (except some intensivists). It is, therefore, unclear whether starvation is beneficial in the setting of 'modern medicine'. Starvation has a number of detrimental effects that could outweigh the potential, beneficial effects of starvation.

PERCEIVED BENEFITS OF EARLY ENTERAL NUTRITION

Acute illness and injury results in a severe catabolic state with marked proteolysis and loss of lean body mass [6▪,34▪]. Early nutrition is widely believed to limit this catabolic response [1▪▪]. Lack of enteral feeding results in gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability, depletion of the liver's antioxidant enzymes, and possible translocation of bacteria and/or bacterial products [35]. Gut-associated lymphoid tissue, is a major source of mucosal immunity in human atrophies during starvation [35]. Enteral infusion of nutrients improves enteric blood flow, prevents structural and functional alterations of the gut barrier, maintains mucosal integrity, decreases enteric permeability, and improves local and systemic immune responsiveness [35]. Furthermore, nutrition support attenuates the metabolic response to stress, limits oxidative cellular injury, and favorably modulates the immune response [35–37].

Based on the perceived physiological benefits of enteral nutrition, it is widely believed that delivering early enteral nutritional support reduces disease severity, diminishes complications, decreases ICU length of stay, and favorably impacts patient outcome [2–4]. A meta-analysis of six small trials involving a total of 234 patients in the ICU showed a survival benefit with the immediate initiation of enteral nutrition, as compared with delayed initiation [38]. However, the quality of the individual studies in this meta-analysis was poor which limits the generalizability of this finding [1▪▪]. Observational cohort studies in critically ill patients have shown that delays in the initiation of enteral nutrition and large caloric deficits (difference between required and delivered calories) are associated with worse patient outcomes [39–43]. It is, however, likely that these observational studies are confounded by severity of illness; less sick patients tolerate enteral nutrition better, are more adequately fed, and have better outcomes. Based on the presumed benefits of early enteral nutrition The Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition guidelines [2], as well as the Canadian [3] and French [4] guidelines all recommend that enteral nutrition be initiated within 48 h in the critically ill patient who is unable to maintain volitional intake. Furthermore, the guidelines suggest 'targeting more than 70% of goal calories (25–30 kcal/kg/day) to achieve the clinical benefit of enteral nutrition over the first week of hospitalization.'

RECENT CLINICAL TRIALS CHALLENGE CONVENTIONAL DOGMA

The results of a number of recent RCTs challenge the recommendations of the widely accepted clinical practice guidelines [2–4], and the notion that early feeding targeting normocaloric goals improves patient outcomes. Six RCTs have recently been performed in critically ill patients comparing trophic feeding ($n=2$) and permissive underfeeding ($n=4$) with targeted normocaloric nutrition [44–49]. In the trophic studies, 1359 ± 83 kilocalories (77% of

goal) were provided in the normocaloric group compared with 350 ± 70 kilocalories (20% of goal) in the trophic group during the first week of hospitalization. Patients in the trophic group did not receive supplemental protein. In the permissive underfeeding studies, patients in the normocaloric group received 1246 ± 126 kilocalories (72% goal) compared with 910 ± 73 kilocalories (49% of goal) in the permissive underfeeding group. Three of the permissive underfeeding studies provided additional protein in the hypocaloric group to achieve similar protein intake [44–46]. A meta-analysis of these studies failed to demonstrate an improvement in any clinical outcome in the patients receiving normocaloric nutrition compared with trophic or permissive underfeeding [50▪].

The results of the meta-analysis by Marik and Hooper [50▪] are supported by two studies which compared a 'volume based' feeding strategy (which enhances the delivery of calories and protein) to a conventional feeding approach. Heyland *et al.* [51] performed a prospective, cluster randomized controlled trial to determine the effect of the PEPuP protocol combined with a nursing educational intervention on the outcomes of 1059 critically ill, mechanically ventilated patients in 18 ICUs. Although the proportion of prescribed protein and energy delivered by enteral nutrition was significantly greater ($P = 0.004$) in the intervention ICUs compared with the control ICUs none of the outcome measures investigated, differed significantly between the control and intervention ICUs. Braunschweig *et al.* [52] randomized 78 patients with acute lung injury to a volume-based or standard nutritional protocol. The percentage of energy needs received/day averaged 85% in the volume-based group compared with 55% in the control group. The trial was terminated prematurely by the Data Safety Monitoring Board because of a significantly higher risk of hospital death in the volume-based group (40 versus 16%, $P = 0.02$).

Randomized controlled trials proving that starvation is detrimental to critically ill and injured patients have until recently not been performed. This is likely because of the lack of equipoise by researchers and the notion that such an experiment would be unethical. However, recently the Dutch Pancreatitis Study Group reported the results of the 'Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis study (PYTHON trial)' [53▪▪]; this study comes close to a RCT comparing initial starvation followed by an *ad libitum* diet to early enteral nutrition administered via a feeding tube (similar to the murine sepsis model performed by Murray *et al.* [31]). In this study, patients with acute severe pancreatitis were randomly assigned to nasoenteric tube feeding within 24 h after randomization or to an oral diet initiated 72 h after presentation with tube feeding provided if the oral diet was not tolerated. In the on-demand group, 32 patients (31%) required nasoenteric tube feeding; 72 patients (69%) tolerated an oral diet and did not require tube feeding. There was no difference in any of the outcome variables between the two groups. Furthermore, there was no difference between the levels of C-reactive protein or the systemic inflammatory response score between the groups over the first week, suggesting that early enteral nutrition did not attenuate the inflammatory response. The results of these recent studies strongly challenge the notion that targeted normocaloric enteral nutrition should be started within 24–48 h of ICU admission and that caloric deficit accrued during the first week of ICU stay is associated with worse outcomes.

INTERMITTENT VERSUS CONTINUOUS TUBE FEEDING

The reasons for the lack of benefit of normocaloric over hypocaloric feeding in ICU patients are not entirely clear. It is possible that normocaloric enteral nutrition does not alter the catabolic process or immune response associated with acute critical illness. However, it should be recognized that in all the RCTs (cited above) which failed to demonstrate a benefit from normocaloric enteral nutrition, patients received continuous rather than intermittent enteral nutrition [54▪]. No species eats continuously (day and night) and such an evolutionary design would seem absurd. The alimentary tract and metabolic pathways of humans appear designed for intermittent ingestion of nutrients a few times a day. Humans have evolved as intermittent meal eaters and are not adapted to a continuous inflow of nutrients; normal physiology appears to be altered when this approach is adopted. Continuously, as opposed to intermittent enteral feeding likely limits protein synthesis [54▪]. The gastrointestinal tract is an important endocrine organ with dozens of regulatory peptides being produced by specialized endocrine cells within the gastrointestinal mucosa. These hormones serve complex roles regulating gastrointestinal motility, gallbladder contraction, pancreatic function, and nutrient absorption [55]. The majority of these hormones are secreted within minutes of nutrient ingestion, rise transiently in the circulation with levels falling back to basal levels after termination of feeding. This entero-hormonal response to nutrient ingestion is almost completely abolished following continuous tube feeding [56]. In a randomized crossover

study, Chowdhury *et al.* [57▪] compared bolus with continuous nasogastric feeding in healthy human adults. In this study, bolus feeding led to a significant increase in the concentration of insulin and peptide YY; these variables remained virtually flat in the continuously fed group.

A limited number of studies have been performed comparing continuous to intermittent enteral nutrition [58,59]. Although these studies did not evaluate patient centered outcomes, such as mortality, ventilator-free days, muscle function, or metabolic parameters they demonstrated that this approach is both well tolerated and feasible. Intermittent feeding, may therefore, be preferred over continuous tube feeding in critically ill patients. The optimal amount of calories and protein that should be given with the intermittent approach is unknown, however, we recommend 20–25 cal/kg/day divided into six aliquots given every 4 h [54▪]. In combat troops protein dosing at a minimum of 20 g of high-quality protein every 4–5 h (during waking hours) has been recommended for optimal functional recovery [60]. Although the optimal protein dose and dosing strategy in critically ill patients is unknown, an approach similar to that of combat troops would appear reasonable, and may attenuate the loss of muscle mass characteristic of critically ill patients [34▪].

CONCLUSION

Anorexia with limited nutrient intake is an evolutionary preserved response that may be beneficial during the first 48–72 h of acute illness. In those patients who are unable to resume an oral diet after this time period enteral nutrition via orogastric or feeding tube is recommended. Continuous tube feeding targeting ideal caloric goals have not been proven to improve outcome; such a mode of feeding is unphysiological and likely harmful. That mode of nutritional support which improves patient centered outcomes is yet to be determined.

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