Intermittent versus continuous feeding in critically ill adults

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Purpose of review
Early enteral nutrition is recommended in critically ill adult patients. The optimal method of administering enteral nutrition remains unknown. Continuous enteral nutrition administration in critically ill patients remains the most common practice worldwide; however, its practice has recently been called into question in favor of intermittent enteral nutrition administration, where volume is infused multiple times per day. This review will outline the key differences between continuous and intermittent enteral nutrition, describe the metabolic responses to continuous and intermittent enteral nutrition administration and outline recent studies comparing continuous with intermittent enteral nutrition administration on outcomes in critically ill adults.

Recent findings
In separate studies, healthy humans and critically ill patients receiving intermittent nutrition (infused over 3 h) had improved whole body protein balance from negative to positive. These studies did not have an isonitrogenous control group. A randomized controlled trial of intermittent bolus versus continuous enteral nutrition in healthy humans found that intermittent bolus feeding increased mesenteric arterial blood flow, increased insulin and peptide YY and reduced blood glucose concentration. A randomized controlled trial comparing intermittent bolus to continuous enteral nutrition in critically ill patients did not demonstrate clinically relevant differences in glycemic variability, insulin use or tube feeding volume or caloric intake between the two groups.

Summary
Studies in healthy humans suggest that intermittent nutrient administration, as opposed to continuous, improves whole body protein synthesis. Unfortunately, similarly designed studies are lacking for critically ill patients. Future studies evaluating the impact of intermittent versus continuous nutrition administration on critical care outcomes should take into account factors such as protein quantity, protein quality and delivery route (enteral and/or parenteral). Until further studies are conducted in critically ill patients, a recommendation for or against intermittent nutrition delivery cannot be made.

Keywords
continuous nutrition, critical illness, enteral nutrition, intermittent nutrition, outcomes, protein kinetics

INTRODUCTION
Enteral nutrition is preferred for the critically ill patient unable to maintain volitional intake and is recommended to commence within 24–48 h of ICU admission [1]. Critically ill patients may derive nutritional and nonnutritional benefits of early enteral nutrition, including maintaining gut integrity, sustaining gut immune function and responses and supporting microbiome diversity [2].

Recently, the intensive care medicine research agenda in nutrition and metabolism highlighted several areas of uncertainty in critical care nutrition, one of which was method of enteral nutrition administration [2]. Under this heading, the effect of continuous versus intermittent feeding on outcomes remains unknown. Which enteral nutrition administration method (continuous or intermittent) provides greater nutritional and nonnutritional benefits? Which enteral nutrition administration method is better for achieving protein and energy prescriptions, stimulating protein synthesis and other critical illness outcomes? The critical care nutrition expert panel identified the need for a

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continuous versus intermittent feeding trial as a ‘top 10’ priority study to be done in the next 10 years [2**].

The aims of this review are to provide a brief overview of the differences between continuous and intermittent enteral nutrition, describe the metabolic responses to continuous and intermittent enteral nutrition administration and discuss recent studies comparing continuous with intermittent enteral nutrition administration on outcomes in critically ill adults.

**METHODS OF ADMINISTERING ENTERAL FEEDING**

Enteral nutrition can be administered through numerous methods, including continuous, intermittent, cyclic and intermittent bolus infusions (Fig. 1) [3]. For example, during continuous feeding, an electric infusion feeding pump delivers enteral nutrition at a constant hourly rate, 24-h per day. During cyclic feeding, a feeding pump administers enteral nutrition in less than a 24-h period. For example, enteral nutrition is administered over 18 h, whereas the subsequent 6 h are meant to enhance a patient’s appetite and/or restore gastric acidity. Cyclic administration will not be discussed further. During intermittent feeding, enteral nutrition is administered over 20–60 min every 4–6 h (with or without a feeding pump). Intermittent bolus is a form of nutrition administration where a syringe or gravity pump administers enteral nutrition over 4–10 min multiple times per day [3]. Ideally, numerous factors should be taken into consideration when choosing between intermittent and continuous enteral nutrition administration method. These factors include expected enteral nutrition tolerance, type of formula used, delivery location (gastric or small bowel), nutritional requirements and availability of product and equipment. Rapid syringe bolus was the most common enteral nutrition administration method prior to introduction of infusion pumps [4]. Rapid syringe bolus was associated with sudden gastric distention, nausea and vomiting and put patients at increased risk for regurgitation and aspiration pneumonia [4]. Today, continuous enteral nutrition administration has become the standard of care worldwide [4].

Nutrition experts argue that intermittent nutrient ingestion may be more physiologic, whereas continuous nutrient intake alters normal gut physiology and may be associated with side-effects [4,5]. The effects of intermittent versus continuous nutrition administration on various outcomes will be discussed next.

**FIGURE 1.** Methods of nutrition administration. In continuous administration, an hourly rate is delivered 24 h a day. In cyclic administration, an hourly rate is delivered for less than 24 h, for example, 18 h, followed by 6 h of pause. In intermittent administration, a volume is delivered over 20–40 min multiple times per day. Bolus administration is considered a form of intermittent administration with a volume administered over a shorter period of time. Used with permission from [3].
THE EFFECT OF INTERMITTENT VERSUS CONTINUOUS FEEDING ADMINISTRATION ON OUTCOMES

Protein synthesis
In health, protein intake is followed by protein synthesis and muscle breakdown occurs between meals to maintain stable muscle mass and net neutral nitrogen balance. Conditions leading to critical illness, such as sepsis, burns and trauma, induce metabolic stress. Metabolic stress increases neuroendocrine, immune, inflammatory, adipokine and gastrointestinal pathways. Activation of these pathways leads to energy substrate use and proteolysis [6]. Anabolic resistance is the failure of normal anabolic stimuli to induce messenger RNA translation of cellular protein and occurs in critical illness, thought to be due to impaired anabolic response to AA, attenuated insulin-mediated reduction in catabolism, splanchnic AA sequestration and reduced AA, attenuated insulin-mediated reduction in catabolism, splanchnic AA sequestration and reduced muscle AA availability [7]. Leucine, a branched chain AA, is a primary anabolic stimulus for protein synthesis through activation of mammalian target of rapamycin (mTOR). The mTOR complex integrates nutrient signals with anabolic growth factors such as insulin [7*]. The combination of proteolysis, stress-mediated anabolic resistance, immobilization and muscle disuse accelerates the loss of muscle mass and a negative nitrogen balance develops. Negative nitrogen balance has been associated with poor ICU outcomes [8]. Loss of muscle mass has been associated with poor wound healing, muscle weakness, mechanical ventilator dependency, increased risk for nosocomial infection and impaired quality of life [6]. Therefore, achieving optimal protein target, as opposed to total energy target, may be more important to improve ICU-related outcomes. Recent observational studies with large international ICU cohorts have demonstrated that achieving protein target, as opposed to total energy target, was associated with improved mortality among critically ill patients who remained in the ICU for at least 4 days [9**,10]. Worldwide, ICU patients achieve approximately 60% of recommended protein intake [11*]. Falling short on protein delivery is important to acknowledge because emerging data suggest that protein may be the important energy component and getting to protein goal may take priority, although the time to protein goal and optimal type of protein are not clear [7*].

What is the effect of intermittent versus continuous nutrition administration on protein synthesis?
Animal data suggest that muscle protein synthesis is rapid, within 30 min, and is sustained for approximately 90 min–2 h, favoring intermittent nutrition administration [12,13]. A three-phase postprandial synthetic response has been proposed. First, after the onset of aminoacidemia, a latent period exists to allow for accumulation of intracellular AA and protein synthesis. Second, protein synthesis lasts for about 90 min. Finally, the onset of the ‘muscle full’ state restores basal protein synthesis (irrespective of continuous AA availability) [4].

Older animal and human studies suggest that protein synthesis is increased with intermittent feeding [4]. In a neonatal pig model, Gazzaneo et al. [12] found twice as much protein synthesis in pigs receiving intermittent bolus protein, as compared to continuously fed pigs. In healthy humans, Bohe et al. [13] measured protein synthesis stimulus latency and duration during a continuous AA infusion and found that muscle protein synthesis rate increased after 30 min and peaked at 2 h despite continued AA infusion, suggesting a saturable effect of protein increased protein synthesis, which returned to baseline after 2 h despite continued AA infusion.

More recently, Rooyackers et al. [14] showed that healthy volunteers receiving parenteral AA intermittently infused over 3 h had improved whole body protein balance. Codere-Maruyama et al. [15] randomized post cardiac surgery patients to receive hyperinsulinemic normoglycemic therapy with or without continuous AA infusion and found improved whole body protein balance in the group receiving continuous AA infusion. Thereafter paucity of data supporting the benefit of intermittent AA infusion on protein kinetics in critically ill patients. Liebau et al. [16] intermittently infused parenteral AA over 3–13 h enterally fed critically ill patients during the first week of ICU admission. The extra parenteral AA improved whole body protein balance (from negative to positive) by increasing protein synthesis. Seven of 13 patients were studied twice and the effect of intermittent parenteral AA administration on protein synthesis was reproduced 3–4 days later [8]. Liebau et al. [17] conducted a pragmatic study to study the effects of continuous enteral nutrition (over 24 h) in critically ill patients and found that administered enteral protein was retained in the splanchnic circulation, postulating the gut kept the protein for itself. In addition, the study also showed a small amount of continuously delivered enteral nutrition improved protein balance.

It is important to mention that protein kinetics data from animals, healthy humans and small numbers of critically ill patients must be inferred with temperance. First, studies showing improvement in protein synthesis with intermittent nutrition delivery used parenteral AA. Second, the effect of intermittent versus continuous AA infusion (stratified by delivery method, enteral and/or parenteral) on protein kinetics in critically ill patients is largely
unknown. Third, the impact of protein quality (whey versus casein) infused intermittently or continuously on protein kinetics in critically ill patients remains unknown. Finally, protein kinetic studies reported whole body protein balance, not muscle protein balance, the latter which may be more pertinent for functional recovery. Larger trials specifically studying the effects of both intermittent versus continuous enteral and/or parenteral nutrition and the effect of whey versus casein-based protein on acute and sustained protein synthesis are needed.

Other outcomes
The method of feeding administration has been shown to impact numerous other outcomes. Some experts contend the entero-hormonal response to nutrient ingestion is abolished during continuous feeding [4,5]. Cholecystokinin (CCK) release following enteral fat intake leads to gall bladder emptying. Intermittent feeding has been shown to result in pulsatile CCK release, whereas continuous feeding has blunted CCK, with findings of an enlarged noncontractile gall bladder [4]. Incretins, such as glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), coordinate ingested carbohydrate load responses [4]. GLP-1 and GIP receptors are found on many organs, including skeletal muscle, where the hormones play a role in coordinated muscle synthesis [4]. Animal models suggest that continuous enteral nutrition, as compared to intermittent bolus enteral nutrition, reduces GLP-1, which may contribute to organ dysfunction [4]. In a recent randomized controlled crossover study, Chowdhury et al. [18] randomized healthy humans to intermittent bolus or continuous enteral nutrition and found that intermittent bolus feeding led to increased mesenteric arterial blood flow and increase in insulin and peptide YY, whereas these two hormones were significantly lower in the continuously fed group. Blood glucose concentration was lower in the intermittent group (over 4 h) [18].

Continuous feeding has been postulated to impair autophagy. Autophagy serves two main roles. First, it is a (physiologic) housekeeping process to mitigate oxidative stress by removing unfolded protein, viruses, bacteria and/or large organelles. Second, autophagy provides a survival mechanism in which AA are recycled for adenosine triphosphate production [19]. Continuous feeding, especially greater calories and AA mTOR stimulation, may impair autophagy. The benefit of autophagy may be limited in severe critical illness and should not be used to direct therapy for three reasons. First, autophagy is time-dependent and operates very early in critical illness. Second, autophagy is a severity-dependent phenomenon [11*]. With greater severity of critical illness, the same stimulatory factors which lead to excessive autophagy also promote cell death [11*]. Finally, autophagy operates in the absence of nutrients and providing nutrients (even continuously) may result in much greater ATP and protein synthesis than autophagy [11*,19].

Since 1986, four randomized controlled trials have compared intermittent bolus to continuous enteral nutrition in critically ill patients [3]. Two trials reported no differences in complications such as aspiration, pneumonia and diarrhea [3]. One trial randomized 18 multiple trauma patients (injury severity score >20) to intermittent bolus or continuous enteral nutrition and found greater interruption in enteral nutrition delivery because of high gastric residual volume, greater diarrhea and greater aspiration in the intermittent bolus group (P values not provided) [3]. More recently, Evans et al. [20] randomized 60 critically ill adults to continuous or intermittent bolus enteral nutrition and found no clinically relevant differences in glycemic variability, insulin use or tube feeding volume or caloric intake between the two groups. Only one trial reported ICU length of stay and ICU mortality (no differences) [3]. Variability in intermittent feeding protocol, patient population, intermittent bolus feeding protocol, follow-up time and the reported outcomes limits generalizability. Furthermore, patient-centered outcomes such as activities of daily living and ability to return to work were not evaluated [21*].

CONCLUSION
Critical illness is associated with accelerated substrate use and proteolysis, culminating in a significant caloric deficit and muscle wasting, respectively. Early enteral nutrition is recommended as a form of primary therapy to mitigate the adverse consequences of heightened inflammation. Continuous infusion remains the most common method of enteral nutrition administration; however, nutrition experts have called into question its benefit. Instead, intermittent enteral nutrition administration is gaining traction. Studies in animals and healthy humans suggest that intermittent nutrient administration, as opposed to continuous, improves protein synthesis and other outcomes such as preservation of autophagy and maintaining the entero-hormonal response to luminal nutrients. Unfortunately, studies with similar methodologies are lacking in critically ill patients. Randomized controlled trials comparing intermittent bolus with continuous enteral nutrition have significant heterogeneity in patients studied, methodology and outcomes reported, which limits
external generalizability to all critically ill patients. Future studies evaluating the impact of intermittent versus continuous nutrition administration on outcomes (such as protein synthesis) should take into account variables such as quantity and type of protein delivered and delivery route (enteral and/or parenteral). Until larger studies with less heterogeneity are conducted, a recommendation for intermittent enteral nutrition or against continuous enteral nutrition cannot be provided.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
■ of outstanding interest


This article outlines critical care nutrition priorities for the next 10 years.


This article was a result of the International Protein Summit and specifically addresses ICU-related effects on protein kinetics and metabolism.


This study uses an international database to identify outcomes associated with greater nutritional intake in critically ill patients stratified by nutritional risk. Greater protein provision in high nutritional risk was associated with improved mortality.


This article outlines the current paradigm in ICU nutrition outcomes, methodologic issues in study design and argues for a combined approach optimizing both nutrition and exercise to optimize muscle mass, strength and physical function.