Influence of nutrition therapy on the intestinal microbiome

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Purpose of review
This review describes the relationship between nutritional therapies and the intestinal microbiome of critically ill patients.

Recent findings
The intestinal microbiome of the critically ill displays a near complete loss of health-promoting microbiota with overgrowth of virulent healthcare-associated pathogens. Early enteral nutrition within 24 h of admission to the ICU has been advocated in medical and surgical patients to avoid derangements of the intestinal epithelium and the microbiome associated with starvation. Contrary to previous dogma, permissive enteral underfeeding has recently been shown to have similar outcomes to full feeding in the critically ill, whereas overfeeding has been shown to be deleterious in those patients who are not malnourished at baseline. Randomized clinical trials suggest that peripheral nutrition can be used safely either as the sole or supplemental source of nutrition even during the early phases of critical care. The use of probiotics has been associated with a significant reduction in infectious complications in the critically ill without a notable mortality benefit.

Summary
Focus of research is shifting toward strategies that augment the intestinal environment to facilitate growth of beneficial microorganisms, strengthen colonization resistance, and maintain immune homeostasis.

Keywords
diet, enteral nutrition, intestinal microbiome, parenteral nutrition, probiotics

INTRODUCTION

With the recent explosion of interest in microbiome research and introduction of new analytic technologies and culture-independent sequencing methods, we have learned an immense amount of information regarding the human intestinal microbiome. We are beginning to uncover the countless loops of interaction that exist between the resident microbes and their human host. We now know that human health hinges on the community structure and function of these microbes and the delicate balance established through our co-evolution. In the absence of physiologic stressors, the healthy intestinal environment is rich in nutrients derived from our diet and further processed by our microbial counterparts, allowing both host and microbe to flourish. Commensal bacteria are not only critical to host metabolism but also to immune homeostasis, strengthening the epithelial cell integrity, regulating proinflammatory pathways, and providing colonization resistance against invading pathogens [1▪,2]. We now know that many disease processes spanning all organ systems are associated with compositional and functional derangements of the gut microbiome. The role of intestinal microbes in the pathogenesis of critical illness progression is becoming more evident. Although, the human gut has been long considered the driver and perpetuator of systemic inflammatory response, the specific role of intestinal bacteria in the pathogenesis of critical illness, sepsis, and multiple organ dysfunction

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KEY POINTS

- Diet has a profound impact on gut microbial composition and function and the intestinal microbiome plays a crucial role in host energy metabolism.
- In the absence of physiologic stressors, the healthy intestinal environment is rich in nutrients derived from our diet and further processed by our microbial counterparts, allowing both the host and its microbes to flourish.
- Physiologic changes associated with critical illness lead to profound compositional and functional changes of the intestinal microbiome, which in turn can be associated with immune activation and progression to organ failure.
- Early enteral nutrition within 24 h of admission to the ICU has been advocated by recent guidelines; however, parenteral nutrition can be used safely either as the sole or supplemental source of nutrition even during the early phases of critical care.
- New therapeutic strategies are needed that restore microbial ecology of the intestine and thwart microbial virulence activation, rather than indiscriminately ridding the intestine of microbes.

syndrome (MODS) has only recently been appreciated [3,4▪▪]. New avenues of critical care research are prioritizing novel therapeutic strategies to restore microbial ecology of the intestine and thwart microbial virulence activation.

GUT MICROBIOME AND ENERGY METABOLISM

The human gut microbiome comprised a vast number of microbes, containing 100-fold more genes than the human genome. The countless metabolic functions existing within this genetic reservoir provide tremendous benefits to humans. For example, the microbiome generates important vitamins essential to our health [5]. Many studies have reported on the importance of bacterial fermentation of plant saccharides such as xylan-containing and pectin-containing carbohydrates to generate short-chain fatty acids (SCFAs) such as butyrate, the primary energy source for colonocytes [6▪]. These byproducts of commensal bacterial metabolism have been shown to be critical for maintenance of epithelial cell integrity and regulation of intestinal and systemic immune responses [7,8]. Importantly, butyrate-producing microbes are often depleted in the gut of the critically ill patients [9▪▪].

Recent studies highlight the crucial role of the gut microbiome in host energy metabolism. Looking at surgically altered intestinal microbiome following weight-loss surgery, Tremaroli *et al.* [10] demonstrated that the composition of the microbiome directly affects the amount of energy extracted from the diet. The authors showed that fecal transplantation of stool from patients that underwent weight-loss surgery into germ-free mice resulted in the mice gaining less weight relative to those receiving fecal transplantation from obese controls. Furthermore, the authors observed stark compositional and functional changes in the gut microbiome following weight-loss surgery, characterized by a shift away from SCFA production and toward amino acid fermentation and bile acid metabolism, indicating reduced energy harvest from the diet.

The intestinal microbiome also plays an essential role in bile acid and fat metabolism [11]. In a study evaluating this microbe–host relationship, Joyce and Gahan show that gastrointestinal microbial expression of bile salt hydrolase, an enzyme responsible for bile acid deconjugation, has the potential to dramatically alter plasma bile acid profile resulting in weight loss and concomitant reduction in cholesterol and triglyceride levels.

EFFECT OF DIET ON THE COMPOSITION OF THE INTESTINAL MICROBIOME

Numerous recent studies show the profound impact of diet on the composition of the intestinal microbiome. In one such study, David *et al.* [12] show that consumption of entirely animal-based or plant-based diet significantly alters the microbial community structure of the gut microbiome. Bacteria with genetic capability to metabolize the components of a given diet and survive within that particular environment are able to proliferate. For example, predominantly animal-based diet is associated with bloom of bile-tolerant microbes and decreased levels of bacteria proficient at plant polysaccharide metabolism. Wu *et al.* [13] surveyed long-term dietary habits from healthy volunteers and found over 80 associations between particular nutrients in the diet and microbiome configurations. Phyla positively associated with a fatty diet and negatively associated with fiber were predominantly composed of Bacteroidetes and Actinobacteria, whereas Firmicutes and Proteobacteria showed the opposite association.

A related consideration is that nutritional excess is a potent determinant of gut microbial composition. A high-fat diet and obese phenotype have both been repeatedly shown to associate with a microbial shift toward increased Firmicutes and Proteobacteria phyla and decreased Bacteroidete

in the intestines of both mice and humans [14,15]. At the same time, weight loss achieved through fat or carbohydrate restriction reverts this compositional ratio back to its original configuration.

Commonly used enteral formulas contain basic ingredients such as corn syrup and triglycerides alongside several synthetic ingredients including dietary emulsifiers. Dietary emulsifiers, such as carboxymethylcellulose, soy lecithin, gum Arabic, soy polysaccharide, and various glycerol derivatives are added to these formulations to extend their shelf-life and texture; however, they have been associated with intestinal dysbiosis. Chassaing *et al.* [16▪] found that two common dietary emulsifiers, carboxymethylcellulose and polysorbate-80, reduced the alpha diversity and microbial stability of the intestinal microflora. The authors specifically saw an increase in the Verrucomicrobia and Proteobacteria phyla in mouse intestine. This altered microbial composition was directly associated with low-grade intestinal inflammation, adiposity, and metabolic syndrome in wild-type mice, as well as severe colitis in $IL10^{-/-}$ and $TLR5^{-/-}$ mice.

DERANGEMENTS OF THE INTESTINAL MICROBIOME IN CRITICAL ILLNESS

The human gut along with its resident microbes has been considered by some to be the driver and perpetuator of systemic inflammatory response in critical illness, sepsis, and associated organ failure [3,4▪▪]. Physiologic changes associated with critical illness in combination with medical interventions such as restriction of oral intake, administration of parenteral nutrition, broad spectrum antibiotics, acid-reducing medications, vasoactive drugs, and opioids impose selective pressures that lead to changes in the composition and function of the intestinal microbiome. These changes are further associated with profound immune activation, which may further predispose to the development of systemic complications [1▪,17▪].

Research has shown that the intestinal microbiome of the critically ill displays a near complete loss of health-promoting microbiota with overgrowth of healthcare-associated pathogenic microorganisms with high-virulence potential [18,19▪▪,20▪▪]. McDonald *et al.* [20▪▪] characterized the intestinal microbiome of 115 critically ill patients at two separate time points following admission to the ICU. The authors found that regardless of the cause of critical illness, the gut microbiome community structure is significantly disrupted and this dysbiosis worsens over time in the ICU. We have also recently characterized the microbiota of critically ill patients and similarly showed a loss of diversity in addition to a loss of the unique microbial signatures of different body sites, which were more likely to be dominated by pathogens [21▪]. Furthermore, the reduction of intestinal microbial diversity has been shown to be predictive of mortality in the critically ill [8]. Earley *et al.* [22▪] show that following burn injury the diversity of the microbiome undergoes significant changes, with alterations of the intestinal microbiome as early as the first day of postinjury, characterized by the overgrowth of Gram-negative aerobic bacteria and associated increase in intestinal permeability. Hayakawa *et al.* [23] describe similar microbiome derangements in otherwise healthy individuals that occur as soon as within 6 h following acute injury such as trauma or cardiac arrest.

Changes in the intestinal microbiome of the critically ill are not limited to the compositional alterations described earlier. With the resulting loss of colonization resistance, invasion of healthcare-associated pathogens and changing intestinal milieu because of nutrient depletion and stress-related host signals, it is not surprising that the resulting ICU microbiome undergoes stark functional changes through the process of virulence activation [1▪,24]. This compositional and phenotypic shift of the intestinal microbiota may be in part responsible for the pathoadaptive immune response of critical illness, sepsis, and MODS [25▪▪].

As plethora of evidence suggest that critical illness and associated medical interventions are responsible for intestinal dysbiosis, the initial state of one's microbiome also plays a role in determining the severity of systemic injury in critical illness [26]. Prescott *et al.* [27▪] show that the degree of probable microbiome perturbation (assessed by the reason for hospitalization) is associated with greater risk of developing subsequent severe sepsis. Whether the critical illness-associated intestinal dysbiosis and the breakdown of the homeostasis between the commensal microorganisms, intestinal epithelium, and the immune system are the cause or the result of progression of critical illness remains to be determined [28]. Likely, components of each co-exist.

EFFECT OF NUTRITIONAL SUPPORT ON THE INTESTINAL MICROBIOME OF THE CRITICALLY ILL

The catabolic state of a critically ill patient leads to substantial losses of lean body mass that are associated with poor clinical outcomes [29]. Lack of enteral nutrition, not uncommon in the ICU, has been shown to not only alter the intestinal microbiome composition, but also to weaken the epithelial barrier function and predispose to

bacterial translocation and associated septic complications [30▪▪,31▪▪]. Early enteral nutrition within 24 h of admission to the ICU has been advocated by recent guidelines to avoid the above changes associated with enteral starvation [32▪▪]. Contrary to previous dogma, permissive enteral underfeeding was recently shown to have similar outcomes to full feeding in the critically ill, whereas overfeeding was shown to be deleterious in patients who are not malnourished [33▪▪–35▪▪].

Although the benefits of enteral nutrition are undisputed, many critically ill patients are intolerant to enteral nutrition. In these patients, parenteral nutrition has been a life-saving supportive treatment. Early research associated parenteral nutrition with high rates of complications, specifically those of infectious nature and current guidelines do not recommend initiating parenteral nutrition earlier than 7 days from onset of acute illness [36▪▪]. Parenteral nutrition has long been thought to be associated with dysbiosis of the intestinal microflora, dysfunction of the intestinal innate immune system, and decreased barrier function of the intestinal mucosa [31▪▪,37,38]. Wan *et al.* [39▪▪] recently confirmed this notion in a mouse model of parenteral nutrition compared with parenteral nutrition with varied levels of supplemental enteral nutrition. The authors noted that parenteral nutrition changes the composition of intestinal microbiota with increased percentage of Bacteroidetes and significantly impairs the intestinal barrier function and innate immunity as judged by the loss of lysozyme, mucin 2 (MUC2), and intestinal alkaline phosphatase (IAP). Interestingly, the authors show that supplementation of 20% enteral nutrition to the regimen has the ability to reverse these untoward changes.

Nevertheless, the superiority of enteral nutrition over parenteral nutrition in critical illness in terms of outcomes has recently become a topic of controversy. Contrary to previous beliefs, human trials suggest that parenteral nutrition can be used safely either as the sole or supplemental source of nutrition even during the early phases of critical care [29,40▪▪,41]. This is in part due to improved central line infection control and more sophisticated total parenteral nutrition (TPN) formulations, and also due to our realization that caloric excess is actually detrimental in critical illness. To this point, Harvey *et al.* [42] demonstrated that patients randomized to targeted nutrition delivery via parenteral nutrition as compared with enteral nutrition within 36 h of admission to the ICU have similar 30-day mortality and adverse events, including infectious complications. A recent systematic review with meta-analysis looking at 18 randomized controlled trials (RCTs) revealed that enteral nutrition was associated with significant reduction in infectious complications only for the subgroup of RCTs in which the parenteral nutrition group received significantly more calories than enteral nutrition group; no effect was seen in trials wherein enteral nutrition and parenteral nutrition groups had a similar caloric intake [43▪▪]. Many of the earlier studies indicating deleterious effects of parenteral nutrition on the intestinal homeostasis have been criticized for excess caloric delivery [36▪▪]. Research is urgently needed to reassess the effects of targeted parenteral nutrition on the intestinal integrity and intestinal microbiome ecology.

CAN WE PROTECT THE INTESTINAL MICROBIOME DURING CRITICAL ILLNESS?

Given that intestinal microbes have the ability to augment their behavior and virulence in response to the local environment, more research is needed to thwart microbial virulence activation and restore microbial ecology of the intestine. Such an idea is distinct from strategies to indiscriminately eliminate gut microbes that hold the potential to select for multidrug resistant pathogens, for example, gut decontamination or broad spectrum antibiotic therapy [1▪,4▪▪]. The idea of supporting the growth of beneficial microorganisms to maintain immune homeostasis and strengthen colonization resistance is logical. Attempts to repopulate the health-promoting microbiota through the use of probiotics, prebiotics, and synbiotics as well as to restore the nutritional homeostasis of the intestinal milieu have shown some promise. However, our knowledge of the complex interactions of the gut microbiome with the epithelium and the immune system during critical illness is still in its infancy. Given our lack of complete understanding of these relationships, it is not surprising that we have been unable to fully harness the power of commensal microbes to promote health.

A recent systematic review and meta-analysis of 30 RCTs involving 2972 ICU patients indicated that administration of probiotics was associated with decreased rates of infection, specifically ventilator-associated pneumonia (VAP). However, there was no effect on mortality, length of hospital stay, or diarrhea [44▪▪]. Interestingly, subgroup analysis showed that the greatest improvement in infectious outcomes was in the group receiving probiotics alone and not synbiotic mixtures. Furthermore, the authors noted a reduction in antibiotic use in patients receiving probiotics. A recently published RCT by Zeng *et al.* [45▪▪] confirmed reduced rates of microbiologically confirmed VAP in patients

randomized to receive probiotics. Although probiotics have been associated with reduction in mortality in animal studies [46], this has not been observed in human clinical trials. The available studies are plagued by differences in the type and dosages of probiotics studied and are, therefore, very difficult to compare. Concerns exist regarding the possible risks of adverse reactions and transfer of antibiotic-resistance genes associated with probiotic use. In fact, a large multicenter RCT (PROPATRIA) published by Besselink *et al.* [47] showed that the use of probiotics in critically ill patients with severe acute pancreatitis was associated with increased mortality when compared with placebo. However, this study ought to be interpreted with caution as problems with the design of the study (such as data management and procedural issues) and ethical concerns (such as no explanation for the unexpected deaths, issues with informed consent and patient privacy) limit its validity. An extreme form of a synbiotic treatment is fecal microbiota transplant, which in limited case reports has shown promise as a targeted microbial therapy in critical care [48]. Finally, another strategy to rescue the microbiome during critical illness is to alter the intestinal environment itself in order to reduce nutritional selective pressures on gut microbes. In one promising example, nutrients such as inorganic phosphate were embedded into the intestinal milieu to decrease bacterial virulence in animal models of critical illness [49,50].

CONCLUSION

This review highlights the complex interplay that exists between nutrition, intestinal microbiome, and the physiology of the human host in critical illness. We are beginning to appreciate how diet and the microbiome converge to impact host energy metabolism. Physiologic changes associated with critical illness impose selective pressures that lead to profound changes to the composition and function of the intestinal microbiome. These changes can lead to further immune activation and development of systemic complications. Research has shown that the intestinal microbiome of the critically ill displays a near complete loss of health-promoting microbiota with overgrowth of healthcare-associated pathogens. Lack of enteral nutrition, not uncommon in the ICU, has been shown to not only alter the intestinal microbiome composition, but also to weaken epithelial barrier function and predispose to bacterial translocation. Contrary to previous dogma, permissive enteral underfeeding has similar outcomes to full feeding in the critically ill, whereas overfeeding is deleterious in those patients who are not malnourished at baseline. Although the benefits of enteral nutrition are undisputed, many critically ill patients intolerant to enteral nutrition benefit substantially from parenteral nutrition. New human trials suggest that parenteral nutrition can be used safely either as the sole or supplemental source of nutrition even during the early phases of critical care. Ultimately, the goal of gut microbiome research in critical illness should be to establish clear mechanistic links between the microbiota and clinical outcomes. If these patterns can be defined, interventions such as probiotics and fecal microbiota transplantation can be targeted to optimize outcomes. Real-time microbiome monitoring will likely emerge in the near future, making it possible to modify the microbiome with precision [50]. Additionally, there is a need to transition from small descriptive studies of the ICU microbiome to well-powered studies documenting the impact of rationally designed interventions.

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Conflicts of interest

There are no conflicts of interest.

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