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The microbiome and nutrition in critical illness

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Abstract

Purpose of review—This review aims to describe the relationship between nutrition and the gut microbiome in critical illness.

Recent findings—Critical illness disrupts not only cells of human origin but also the intestinal microbiome, with a decrease in bacterial diversity and transformation into a pathobiome. Under basal conditions, nutrition profoundly alters microbial composition with significant salutatory effects on human health. In critical illness, enteral nutrition is recommended and has theoretical (but not proven) advantages towards improved inner microbial health and diminution of bacterial translocation. Dietary supplements such as probiotics and fiber have been shown to improve microbial derangements in health. However, their impact on the microbiome in critical illness is unclear and while they may have some beneficial effects on patient-centric outcomes, they do not alter mortality. The precise mechanisms of how nutrition and dietary supplements modulate the gut microbiome remain to be determined.

Summary—Nutrition and supplements such as probiotics appear to play a significant role in modulating the microbiome in health, yet the relationship in critical illness is unclear. Further investigation is required to determine the mechanistic determinants of the impact of nutrition on the microbiome in critical illness and the potential clinical implications of this.

Keywords

Microbiome; pathobiome; ICU; nutrition; probiotics

INTRODUCTION

The relationship between the human host and a vast microbial world residing within is both dynamic and symbiotic. Trillions of bacteria reside on our skin and respiratory, genitourinary and digestive tracts (1) with a continuous complex conversation between human and microbial cells that is crucial to the health of both. The gut contains the highest abundance of microbes, where a variety of commensal bacteria coexist with viruses and

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fungi. Techniques such as 16S rRNA sequencing with metagenomic analysis have helped to uncover the genotypic and phenotypic signatures that these bacteria possess beyond what simple cultures provide (2). Under basal conditions, the gut microbiome plays pivotal roles in multiple processes including (but not limited to) immune system modulation, substrate metabolism, and neurologic processes. However, when the human host is injured, the microbiome is also deleteriously impacted with the development of a pathobiome, containing a higher proportion of potentially pathogenic bacteria, with simultaneous development of new virulence factors in previously commensal bacteria (3). The development of the pathobiome has been proposed to negatively impact many of the same processes it benefits in the setting of health (4). Numerous factors directly and indirectly alter the microbiome in health and illness including intrinsic factors that cannot be manipulated (genetics, age) and those that can be manipulated by either a human host or a medical team caring for a patient (diet, geography, drug therapy) (5–7). The relationship between nutrition and the microbiome has drawn significant attention from scientists who hope to define the nutrients that maintain a homeostatic microbiome under basal conditions and that could potentially preserve or restore a healthier microbiome during acute illness. The gut has long been hypothesized to be the “motor” of multiple organ dysfunction syndrome in critical illness (8). While the reasons behind this are complex, crosstalk between the gut epithelium, immune system and the microbiome can have profound effects both locally and systemically during critical illness (9). Enteral nutrition has beneficial effects on host immunity during critical illness, decreases villus atrophy and theoretically protects from bacterial translocation through maintaining gut integrity. While significant evidence supports the role of nutrition in the maintenance of the gut microbiome in health, relatively little data examines this link in critical illness.

THE GUT MICROBIOME

Next-generation sequencing technology has allowed for identification of the contents of the gut microbiome in multiple physiologic and pathologic human and animal models. Of the seven phyla that compose the commensal bacteria in the intestine, two phylogenic types dominate: *Firmicutes* and *Bacteroidetes* (10). The majority of the species that occupy the gut play a beneficial role in human health while keeping harmful microbiota in check that have the potential themselves to shift to a virulent state (11).

Under basal conditions, health-promoting microbiota play a myriad of essential roles in maintaining host metabolism, immune competence, gut integrity, colonization resistance, etc. (12). For example, production of essential short-chain fatty acids -- the primary energy source for the intestinal epithelial cell while promoting the growth of the healthy gut microbes -- is reliant on intestinal microflora metabolism. In addition, the microbiome and immune system interact heavily. This is shown most clearly in germ-free mice, which lack all commensal bacteria. These animals fail to develop a mature immune system are susceptible to pathogenic viruses, bacteria, and fungi (13, 14), underscoring the importance of the microbiome’s role in immune system development and capacity to respond to infectious insults.

THE PATHOBIOME IN CRITICAL ILLNESS

Numerous factors lead to the development of the pathobiome in critical illness. The overall pathologic milieu of critical illness alone induces profound changes to the pathobiome, within hours of admission to the intensive care unit (ICU) (15–17). This is exacerbated by a number of interventions designed to benefit the patient but which also have significant effects on the microbiome in isolation. Examples of medications that profoundly alter the microbiome include (but are not limited to) antibiotics, opioids, and proton pump inhibitors (18) (19) (20). The pathobiome in turn, can potentially accelerate a dysregulated host response leading to exacerbation of organ failure.

Recent studies examining ICU patients have displayed low alpha (in-group) microbial diversity and large beta (between group) diversity, with a gradual worsening of dysbiosis throughout the course of ICU stay (21–24). The largest study conducted to date examined 16S rRNA gene sequencing of skin, oral and stool samples from 115 ICU patients and compared them to 1242 healthy patients (23). The results revealed a low abundance of *Firmicutes* and *Bacteroidetes* and an increased abundance of *Proteobacteria* in comparison to healthy individuals. Remarkably, changes to the microbiome have been identified within 6 hours of ICU admission for non-infectious insults such as cardiac arrest and multiple trauma (16). Changes identified in critically ill patients include depletion of butyrate-producing microbes in critically ill patients with a subsequent overgrowth of virulent strains of *Escherichia*/*Shigella*, *Salmonella*, *Enterococcus*, *Clostridium difficile* or *Staphylococcus* (25). It has been proposed that serial changes in the *Firmicutes*/*Bacteroidetes* ratio can potentially predict patient outcomes (21) although additional work is required to validate this. Further, critical illness is associated with a development of ultra-low diversity. A study of 34 ICU patients demonstrated a single bacterial genus made up more than 50% of the gut microbiota in more than a third of patients (26). This is consistent with a smaller study of 14 ICU patients demonstrating ultra-low diversity in 35% of patients, containing only 1–4 bacterial taxa (22). Further, a study of critically ill trauma patients with a mean injury severity score of 27 showed no difference compared to uninjured patients at time of presentation. However, trauma patients rapidly developed significant alterations in phylogenetic composition and taxon relative abundance with depletion of bacterial orders *Bacteroidales, Fusobacteriales* and *Verrucomicrobiales* and enrichment of *Clostridiales* and *Enterococcus* (27). A comparison of 37 pediatric ICU patients to both pediatric and adult reference datasets demonstrated decreased alpha diversity in the gut and significant differences in beta diversity at multiple body sites in critically ill children (28). Further, pathogenic gut bacteria were enriched at multiple body sites with diminution of health promoting gut bacteria. The lung microbiome is also altered following sepsis and ARDS, and notably the lung microbiome is enriched with gut bacteria, suggesting a potential role of translocation of intestinal contents to distant sites in the setting of critical illness (29).

HOW DOES NUTRITION AFFECT THE GUT MICROBIOME?

Specific nutrient types (carbohydrates, lipid, and protein) affect the microbiome in disparate ways in animal studies, with development of specific species abundance after long-term exposure to diets heavy in one component For instance, diets high in protein and animal fat

lead to an abundance of *Bacteroides* in the gut microbiome versus a carbohydrate-rich diet which leads to *Prevotella* gaining dominance (30). Further, excessive intake of particular nutrients leads to derangements in microbial composition as mice fed a high-fat diet have a decrease in *Bacteroidetes* and an increase in both *Firmicutes* and *Proteobacteria* (31). In addition, an animal-based diet increases the abundance of bile-tolerant microbes and decreases the levels of *Firmicutes* that metabolize dietary plant polysaccharides within 5 days in healthy volunteers (32). Dietary fiber serves as a growth substrate for gut bacteria thus affecting the composition and metabolome of the microbiome. The fiber inulin prevents disruption of the unstirred mucus layer in the gut of mice maintained on high-fat diets (33). In contrast, low fiber intake compromises this layer causing microbial instability with an associated increase in virulent strains and production of potentially harmful metabolites (4). In addition, a study examining the long-term dietary habits of healthy volunteers found that *Bacteroidetes* and *Actinobacteria* were positively associated with fatty diet and negatively associated with fiber whereas *Firmicutes* and *Proteobacteria* showed the opposite association (30). Notably, high fat and obese phenotype was associated with a microbial shift in mice towards increased *Firmicutes* and *Proteobacteria* and decreased *Bacteroidetes* whereas weight loss through fat or carbohydrate restriction reverts back to original configuration (31). In addition, total parenteral nutrition alters the gut microbiome with enrichment of *Proteobacteria,* and the altered metabolomic composition of the gut lumen in mice given total parenteral nutrition promotes dysbiosis (34).

NUTRITIONAL SUPPORT AND THE MICROBIOME IN CRITICAL ILLNESS

Nutrition in critical illness is a complex topic, with conflicting data and recommendations regarding route and timing of optimal nutrition that are outside the scope of this review (35–37). Despite data demonstrating that diet affects the microbiome in health and the frequency of nutritional support in ICU patients, there are negligible experimental or observational data on how route, timing or composition of nutritional support impact the microbiome of critically ill hosts. Of note, parenteral nutrition increased *Bacteroidetes* and impaired barrier function in mice while this effect was reversed by supplementation of 20% enteral nutrition (38).

DO DIEATARY SUPPLEMENTS MODULATE THE MICROBIOME IN CRITICAL ILLNESS

Prebiotics

Prebiotics are essential supplements used to promote the growth of healthy microbiota by providing carbohydrates as fuel and fiber for fermentation. Fiber-rich diets exhibit beneficial effects on intestinal barrier integrity thus maintaining protection against invading pathogens in murine septic models. Mice fed a high-fiber diet with cellulose for two weeks prior to the onset of sepsis demonstrate an abundance of the genera *Akkermansia* and *Lachnospiraceae*, and have improved survival following cecal ligation and puncture. Notably, administration of antibiotics to mice on the high-fiber diet negated both the enrichment in *Akkermansia* and the survival benefit in sepsis (39). Importantly, the effect of additional oligofructose and inulin on gut microbial composition in critically ill patients receiving enteral nutrition was

recently examined (40). Unlike in healthy humans, additional fiber did not increase beneficial fecal *Bifidobacteria* which suggests that the effect of dietary fiber might be blunted in critical illness where the combination of the overall pathologic state combined with antibiotic use negatively impacts the flora that would otherwise thrive in environments of prebiotic availability.

Probiotics

Probiotics are exogenously supplied live microbes. The theory behind probiotic supplementation relies on the concept that seeding the gut with genera thought to be beneficial in the gut or depleted in critical states could help maintain or at least partially restore a healthy microbiome. Probiotics help suppress gut cytokine production, stimulate a protective mucus layer and IgA production, prevent gut apoptosis, protecting the gut barrier, and reduce pathogenic bacterial overgrowth (41, 42). The impact of probiotic supplementation on the microbiome has not been extensively studied in the ICU setting. However, probiotics have been shown to decrease the frequency of ventilator-associated pneumonia without an overall improvement in outcome (43, 44) and are not recommended as standard of care in the ICU (45).

Synbiotics

Synbiotics are the combination of prebiotics and probiotics. Conceptually, synbiotics have the potential benefit of a synergistically positive influence in pathologically altered states. An enteral formula containing synbiotics has been demonstrated to increase *bifidobacteria* in critically ill children while diminishing *Enterobacteria* levels (46). In addition, daily supplementation with synbiotics (*Bifidobacterium breve* strain Yakult, *Lactobacillus casei* strain Shirota, and galactooligosaccharides) in 35 septic patients resulted in a lower incidence of both ventilator associated pneumonia and enteritis as well as increased fecal *Bifidobacterium* and *Lactobacillus* compared to 37 critically ill patients who did not receive synbiotics (47).

Fecal microbial transplant

Outside of the ICU, fecal microbiota transplantation is remarkably effective in treating recurrent *Clostridium difficile* colitis (48) with durable changes in the microbiome after transplantation. However, data in the ICU is restricted to a series of individual case reports (49) and numerous logistical and theoretical concerns must be overcome before this therapy can be given outside of an experimental basis in critical illness.

CONCLUSION

Considering that throughout the entirety of human history we have co-evolved with our inner microbes, there is significant intellectual appeal to the concept of restoring a pathobiome to a healthier microbiome in critical illness. However, despite significant evidence that nutrition directly alters the microbiome in health, data suggesting that nutrition impacts the pathobiome in critical illness are lacking. Further, evidence that targeting nutritional intake as a means for improving the microbiome in the ICU are essentially non-existent currently. Ultimately, both optimal nutrition and therapy targeted at restoring a

healthy microbiome represent attractive avenues for further research. However, determining whether a mechanistic link exits between nutrition and the microbiome in critical illness requires a significantly higher level of understanding than currently exists. The capacity to perform real-time monitoring of gut microbiota (50) in critically ill represents an opportunity to determine in the future whether nutrition can be used as a therapeutic approach – perhaps on a personalized basis -- to target the pathobiome in the ICU.

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KEY POINTS

- Health-promoting microbiota have a myriad of important roles in maintaining host metabolism, immune homeostasis, gut integrity, and colonization resistance.
- In critical illness, the microbiome is converted into a pathobiome, which has the potential to cause and exacerbate organ failure in the ICU.
- The content of the human diet profoundly changes the gut microbiome during health
- Inadequate data exist to understand the impact of nutrition and supplements on the microbiome in critical illness