The microbiome of the critically ill patient

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Purpose of review
Advances in the understanding of the human microbiome outside of the ICU have led investigators to consider the role of the microbiome in critical illness. The picture that is being elucidated is one of dysbiosis occurring at multiple sites in the critically ill patient. This review describes the changes that occur in the various microbiomes of a critically ill patient, the implications of these changes and shows how advances in the understanding of dysbiosis may lead to microbiome-targeted therapies.

Recent findings
Critically ill patients undergo dysbiosis at several organ sites including the skin, gastrointestinal system and the lungs with loss of microbial diversity and a propensity for potentially pathogenic organisms to dominate a particular microbiome. These microbiome changes appear to be predictive of clinical outcome. While the use of fecal microbial transplantation has been demonstrated to be an effective treatment for recurrent *Clostridium difficile* infection, the use of fecal microbial transplantation and other microbiome modifying therapies may have a role in managing critical illness in the ICU.

Summary
A growing understanding of the microbiome in the critically ill may modify current dogma regarding the pathogenesis of sepsis and other life-threatening conditions seen in the ICU, thereby fundamentally changing antibiotic stewardship and the management of the critically ill patient.

Keywords
critical care, dysbiosis, fecal microbiota transplantation, microbiome

INTRODUCTION

The terms 'microbiome' and 'microbiota' refer to all the organisms and the genomes of all the organisms, respectively, that occupy a habitat such as an organ system (Table 1). This distinction in terminology is sometimes ambiguous in the medical literature with 'microbiome' being used interchangeably with 'microbiota'.

Medical manipulation of gut microbiota actually preceded our understanding of the complexity of the various ecosystems that live on or within humans. Beginning in the 1950s, before *Clostridium difficile* was shown to be the causative organism, pseudomembranous colitis was successfully treated with fecal microbial transplantation (FMT) [1]. The development of highly sensitive, nonculture-based techniques (primarily whole-metagenome shotgun analysis or 16S ribosomal *RNA* gene sequencing) has shed light on previously unidentified organisms inhabiting various microbiota. The ongoing development of bioinformatics software (in particular, Quantitative Insights Into Microbial Ecology) has allowed investigators to better define operational taxonomic units within these ecological communities and apply various statistical measures to better describe and compare microbiota. Together, these molecular and statistical techniques have dramatically improved our understanding of the microbiome and dysbiosis to show that colonizing microbes may impact numerous and disparate human conditions including asthma, obesity and mental illness. With the except of newborn infants, however, there has been little study of the microbiome as it pertains to acute disease or hospitalized patients. The purpose of this review is to highlight recent advancements in the understanding of various ICU patient microbiomes and in the application of these findings to the care of critically ill patients.

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KEY POINTS

- In addition to a loss of site specificity, the microbiomes of ICU patients demonstrate a loss of microbial richness and diversity, and tendency for a single taxon (frequently a potential pathogen) to dominate a given microbiome.
- There is an interplay between microbiomes in the critically ill with animal and observational human data suggesting that the gut microbiome may negatively impact the lung microbiome in conditions such as sepsis and acute respiratory distress syndrome.
- Microbiome patterns may be predictive of clinical course among ICU patients.
- How exactly to manipulate the microbiome to improve outcomes in critically ill patients has not been determined. To date, efforts have focused on using fecal microbiota transplant and probiotics to alter the composition of various microbiomes of ICU patients. Alternatively, better antibiotic stewardship or therapeutics such as ribaxamase that serve to limit the systemic reach of antibiotics may prevent the development of dysbiosis.
- It is conceivable that the treatment of critically patients may someday entail the concomitant use of both antibiotics and promicrobiome therapies.

MICROBIOMES OF THE CRITICAL CARE PATIENT

The landscape of the ICU microbiomes is in the early stages of being mapped. Nutrient deprivation, opioid use, vasoactive agents, gastrointestinal (GI) prophylaxis agents and especially liberal antibiotic use have all been shown to impact the gut microbiome of ICU patients [2]. Which of these factors and to what degree each factor may impact other microbiomes of ICU patients has not been exquisitely resolved. In general, microbiomes of ICU patients demonstrate a loss of microbial richness and diversity, a tendency for a single taxon (and oftentimes a potential pathogen) to dominate a given microbiome and a loss of site specificity (i.e. colonization with the same organism at multiple sites) [3▪▪].

Yeh *et al.* [3▪▪] conducted a comprehensive observational study of 32 adult ICU patients admitted for trauma or acute surgery. Samples were collected from multiple body sites within 48 h of admission and then every 3–4 days. Compared with samples from a healthy volunteer database, GI, oral and skin microbiota of ICU patients demonstrated reduced microbial diversity with a relative loss of commensals. ICU patients' microbiota were also more prone to be enriched with potential pathogens including *Enterococcus* in the gut, *Mycoplasma* in the oral cavity and *Acinetobacter* on the skin. Although samples from both healthy and ICU patients commonly demonstrated a dominant taxon, this organism was more likely to be a commensal in health and a potential pathogen in ICU patients. Prior studies have also shown that microbial communities of healthy individuals at different anatomic sites are distinct in composition. In contrast, Yeh *et al.* describe a loss of microbiota site specificity in ICU patients with a single taxon and often a would-be pathogen being observed simultaneously in skin, tongue and GI sample at much higher rates than healthy controls. In general, the dysbiotic observations made across microbiotas in this study were largely replicated in two other observational studies including one study which exclusively enrolled pediatric ICU patients [4,5].

How long ICU dysbiosis persists, the clinical impact of dysbiosis and in which critically ill patients is not fully known. In a study of 107 intubated patients, the authors identified a 'microbial shift' in the dental plaque of 35 patients [6]. The oral microbiome is of keen interest as it may serve as a source of pneumonia and appears to be affected by critical illness and critical care therapies. Using PCR technology, *Staphyloccus aureus* or *Pseudomonas aeruginosa* was identified in the dental plaque of 35 patients. Significantly, postextubation 70 and 55% of patients with plaque colonized with *S. aureus* and *P. aeruginosa*, respectively, reverted to normal flora.

Recent advances in our understanding of the lung microbiome in critical illness deserve separate discussion. Kelly *et al.* [7] performed an observational study of 15 ICU patients intubated for respiratory failure. Like the microbiota at other anatomic sites of ICU patients, the lower respiratory microbiota of critically ill intubated patients was also characterized by reduced alpha diversity that further diminished while receiving mechanical ventilation. Of particular interest though, is a study by Dickson *et al.* [8▪] that highlights the impact of the gut microbiota on the lung microbiome. They performed a two-part study: the first part involved a murine model of sepsis and the second part represented the first culture independent study of the human lung microbiota in 68 patients with acute respiratory distress syndrome (ARDS). The authors show that the lung microbiome in both the murine sepsis and human ARDS was enriched with gut-associated bacteria. One *Bacteroides* operational taxonomic unit was detected in bronchoalveolar fluid (BAL) samples from 41% of ARDS patients compared with 3% of healthy patients. And systemic and alveolar TNF-α levels in patients with ARDS was notably affected by the presence of gut-derived organisms present in BAL fluid. It was

Table 1. Glossary of terms

General	
Microbiome	Collection of all microbioal genomes in a host (including viruses, bacteria, fungi, archae, protozoa)
Microbiota	All microbial genomes in a defined environment (e.g. gut microbiome)
Metabolome	Total content of metabolites in a community of microbiota
Dysbiosis	Condition when normal composition of microbiome has been disrupted and is detrimental to the host
Pathobionts	Species that expand as a result of dysbiosis and exert pathogenic effects on host
Culture independent microbe identification	
Amplicon Sequencing	PCR amplification followed by sequencing of specific DNA markers that define the genome that contains it
16s	Amplification of preserved sequence regions of 16s ribosomal subunit that are unique to prokaryotic cells and therefore identify bacteria
Whole metagenome shotgun analysis	Comprehensively sample all genes in all organisms present in a given complex sample, to evaluate bacterial diversity and detect abundance of microbes
Analytic terms	
OTUs	Cluster amplicon sequences based on similarity threshold as a proxy for species-level taxonomic assignment
Alpha-diversity	In-sample taxonomic diversity (abundance of different taxonomic groups and overall number of taxonomic groups in a microbial community)
Beta-diversity	Taxonomic diversity between samples to describe absolute or relative taxonomic overlap between samples
Therapeutics	
Prebiotics	Dietary substances that favor the growth of beneficial bacteria over harmful ones
Probiotics	Microorganisms that may help the digestive tract return to normal after being disturbed (e.g. antibiotics)
Synbiotics	Combination of probiotics (micro-organisms) and prebiotics (dietary supplements)
Fecal microbiota transplant	Administration of fecal matter from a donor into the intestinal tract of a recipient to directly change the recipient's microbial composition

OTU, operational taxonomic unit.

eye-catching that the precise route by which gut-derived organisms arrived in the lungs of mice with sepsis was not identified as analysis of matched oral and blood specimens was unrevealing.

THE MICROBIOME AS A PREDICTOR OF MORTALITY IN THE CRITICALLY ILL

Microbiota patterns of the critically ill may be predictive of clinical outcomes including mortality. Suggestive of this fact was one study which made the startling observation that the composition of some fecal samples taken from ICU patients resembled those obtained from decomposing corpses [4]. Another single-center investigation prospectively evaluated the changes in the gut microbiome of 12 ICU patients and found that extremes in the ratio of *Bacteroides* relative to *Firmicutes* in stool samples occurred in those who died compared with survivors [9]. Next-generation sequencing technology has also been used to investigate the microbiota of endotracheal tubes (ETTs) to identify markers of patient outcome. In a study of 39 ETTs which were culture positive for both *P. aeruginosa* and *Staphylococcus epidermidis*, the relative abundance of pseudomonas was predictive of survival [10]. Moreover, the ETT microbiota of patients who survived tended to include organisms from the phylum *Actinobacteria*, which included *Bifidobacteria*, a common component of probiotic therapies.

MANIPULATING THE MICROBIOME FOR THE TREATMENT OF SPECIFIC CONDITIONS IN THE ICU

Microbiome-based therapies can be categorized into three groups: FMT, probiotics and synbiotics. FMT represents a promising microbiome-altering treatment for patients with critical illness. FMT has been shown to be an effective therapy for recurrent *C. difficile* infection and has been successfully used to treat severe *C. difficile* infection in one ICU patient [11]. In general, FMT is performed with the intent of restoring the gut microbiota but the

exact mechanism responsible for its effectiveness is not known. A recent review article aptly summarizes possible means by which FMT may function: transplanted microbiota may compete with *C. difficile* for nutrients; commensal bacteria may produce bacteriocins, proteinaceous antimicrobial molecules, against C. *difficile*; restoration of bile acid metabolism by microbiota may inhibit both germination of spores and the growth of vegetative growth of various *C. difficile* strains; and transplanted microbiota may interact with the immune system via complex signaling to repair of gut mucosal barrier [12▪]. A more thorough understanding of which specific microbial components are necessary for restoration of a healthy microbiome is crucial to develop selective fecal microbiome transplants. Probiotics have also been studied as therapies for C. *difficile* without consistent success because this approach likely represents an oversimplified solution to dysbiosis. Nonetheless, both FMT and probiotic and synbiotics have recently been reported as potential microbiota-targeted therapies for a variety of critical illnesses.

Sepsis

Case reports suggest a possible benefit of FMT in the treatment of sepsis with concomitant diarrhea. Wei *et al.* [13] described two elderly stroke patients who had clinical courses complicated by multiorgan failure syndrome, sepsis and severe diarrhea that did not improve with antibiotic therapy, cessation of antibiotics or probiotics (although details of probiotic therapy was not described). The results of stool bacteria culture and *C. difficile* testing were negative for both patients. Compared with the donor stool, the patients' fecal microbiota pre-FMT were notable for lower percentage of *Firmicutes* which – posttransplant – increased to percentages similar to the donor stool. Clinically the patients improved postprocedure with reductions in systemic inflammatory markers, resolution of fever and a return to normal stool frequency and volume by 16 days post-FMT.

These results support an earlier case report of a 44-year-old woman who underwent proximal gastrectomy and bilateral truncal vagotomy for a gastric neuroendocrine tumor [14]. Her postoperative course was lengthy and tumultuous in which she experienced *Acinetobacter baumannii* and *Enterococcus faecalis* bacteremia (which the authors surmise was gut-derived), septic shock and respiratory and renal failure requiring mechanical ventilation, venovenous extracorporeal membrane oxygenation and continuous renal replacement therapy. She received multiple antimicrobial and probiotic (*Bifidobacteria*) therapies. Despite these treatments, her diarrhea and fever persisted. Compositional analysis of the patient's fecal microbiota was performed on postoperative day 25. Compared with a healthy volunteer, the patient's fecal microbiota – on the phylum level – was notable for relatively diminished proportions of *Firmicutes* (16 vs. 52%) and Bacteroidetes (0 vs. 29%), whereas the percentage of Proteobacteria was dramatically increased (78 vs. 16%). Within the family of Proteobacteria, molecular fingerprinting detected the presence of many pathobionts including *Klebsiella pneumoniae*, *Enterobacter* sp. and *A. baumannii*. On postoperative day 30, the patient underwent FMT, and antibiotics were discontinued later the same day. Sixteen days post-FMT, her sepsis and diarrhea had resolved. Her clinical improvement coincided with changes in her fecal microbiota composition with the percentage of *Firmicutes* increasing and Proteobacteria decreasing. Likewise, multiple inflammatory markers including TNF-α, IL-6 and C-reactive protein which were elevated pre-FMT declined substantially posttransplant.

A potential role for synbiotic therapy to *prevent* sepsis in vulnerable patient populations such as the critically ill is suggested by a recent large randomized trial performed in newborn infants performed in rural India [15▪▪]. Approximately, 4500 healthy newborns were randomized to receive a 7-day course of either placebo or an oral synbiotic preparation (*Lactobacillus plantarum* and fructooligosaccharide) and followed for 60 days. The trial was terminated early after a 40% risk reduction of the primary outcome (death or sepsis) was noted in the treatment arm. Importantly, the choice of *L. plantarum* was based on pilot studies which showed superior gut colonization compared with other Lactobacillus strains. Potential differences in the infant and adult microbiome withstanding, these stunning results beg the question of whether the prophylactic administration of a well selected synbiotic therapy could prevent secondary sepsis in ICU patients.

Antibiotic-associated colitis

Wurm *et al.* [16] described a patient who developed antibiotic-associated enterocolitis without evidence of *C. difficile* infection following concomitant administration of broad-spectrum antibiotics and steroids. Endoscopic biopsies demonstrated apoptotic enteropathy on histopathology similar to acute gut graft-vs.-host disease. The patient's gut microbiome was severely depleted with limited diversity and abundance in comparison with normal colonic microbiota. The patient received a FMT on a

compassionate use following 3 months of persistent diarrhea. The effect of therapy was dramatic with clinical improvement and colonic mucosal healing noted on histology 7 days after FMT. Although this is a single case, it suggests that select populations with documented dysbiosis and non-*C. difficile* associated enterocolitis may benefit from FMT to restore normal flora and gut integrity.

Colonization with multidrug-resistant organisms

Nine recent case reports describe the use of FMT to successfully decolonize patients (mostly immunocompromised) harboring multidrug resistant organisms (MDRO) [17,18]. There were no significant adverse effects reported in these cases. Similarly, post-hoc analysis of a microbiota suspension enema trial for recurrent *C. difficile* found that eight of 11 patients who initially tested positive for Vancomycin-resistant *Enterococci* (VRE) were negative for VRE at the conclusion of the study [19]. Currently, there are nine trials listed on clinicaltrials.gov evaluating the potential benefit of FMT to treat MDRO gut colonization as a means of preventing subsequent infection [18,20–23].

Ventilator-associated pneumonia

The benefit of probiotics to prevent ventilator-associated pneumonia (VAP) is unclear and is undoubtedly complicated by the variety of probiotics being studied. A Cochrane review of eight randomized clinical trials (1083 participants) showed that probiotics decreased the incidence of VAP but had no impact on all other reported outcomes including mortality, length of ICU stay or duration of mechanical ventilation [24]. Subgroup analysis was not successful in identifying one particular probiotic as being superior. In a more recent randomized trial involving 235 intubated patients, those who received a probiotic capsule containing live *Bacillus subtilis* and *E. faecalis* did not experience any benefit in terms of the incidence of clinically suspected VAP, duration of mechanical ventilation, mortality or length of hospital stay [25].

Currently, a large randomized trial is enrolling intubated, critically ill patients with the aim of determining the effect of the probiotic *Lactobacillus rhamosus* on the incidence of VAP [26].

PROTECTING THE MICROBIOME IN THE FACE OF SYSTEMIC ANTIBIOTICS

It has been estimated that 51% of all ICU patients are infected and 71% are receiving antibiotics at any given time [27]. Even with judicial antibiotic usage, dysbiosis may be an unavoidable consequence of critically ill patients being treated for a life-threatening infection. Ideally antibiotics would treat an infection at one particular site with minimal impact on neighboring microbiomes. The concominant use of ribaxamase, an oral beta-lactamase, has been proposed as a treatment to protect the gut microbiome in the setting of intravenous beta-lactam administration. Beta-lactam antibiotics are known to dramatically alter the gut microbiome even when administered intravenously as these agents are excreted in the bile and reach the intestine as fully functional antibiotics. In a small study, intravenous ceftriaxone and ribaxamase were concurrently administered to 23 patients with functioning ileostomies (for ease of sampling intestinal chime). The regimen was well tolerated and ribaxamase was shown to effectively degraded intestinal ceftriaxone without altering plasma ceftriaxone pharmacokinetics [28].

CONCLUSION

Patterns of dysbiosis occurring at various microbiomes of critically ill patients are becoming better understood and may be predictive of clinical outcomes. Promising results in microbiome-based ICU therapies, however, must be tempered by the fact that there is potential harm with this approach. In the Probiotic in Pancreatitis Trial, patients with pancreatitis who were treated with a multispecies probiotic preparation incurred a higher mortality rate than patients in the control arm (16 vs. 6%, respectively) [29]. The failure of this study, despite two prior studies showing benefit, emphasizes the need for a rational approach to microbiome-based treatments that accounts for patient selection, concomitant prebiotic use, and strain and dose of probiotic [30,31]. Nonetheless, growing appreciation of the critical illness microbiome has already impacted critical care by highlighting the need for judicious antibiotic usage and stewardship. In the future, critical illness may be treated with equal parts anti and probiotic therapy in an attempt to balance the dangers of infection and sepsis with the harm of dysbiosis.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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