HHS Public Access

Author manuscript

Lancet Respir Med. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Lancet Respir Med. 2016 January ; 4(1): 59–72. doi:10.1016/S2213-2600(15)00427-0.

The microbiome and critical illness

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Abstract

The central role of the microbiome in critical illness is supported by a half century of experimental and clinical study. The physiological effects of critical illness and the clinical interventions of intensive care substantially alter the microbiome. In turn, the microbiome predicts patients' susceptibility to disease, and manipulation of the microbiome has prevented or modulated critical illness in animal models and clinical trials. This Review surveys the microbial ecology of critically ill patients, presents the facts and unanswered questions surrounding gut-derived sepsis, and explores the radically altered ecosystem of the injured alveolus. The revolution in culture-independent microbiology has provided the tools needed to target the microbiome rationally for the prevention and treatment of critical illness, holding great promise to improve the acute and chronic outcomes of the critically ill.

The forgotten organ in multiorgan failure

The common conditions of critical illness (including sepsis, acute respiratory distress syndrome [ARDS], and multiorgan failure) cause tremendous global mortality and an enormous and growing economic burden.[1] Although specialties such as oncology and rheumatology have been revolutionised by the breakthroughs of molecular medicine, decades of research into the diseases of critical illness have yielded no targeted therapies. In practice, critical care remains synonymous with supportive care.

There are several possible reasons why no molecular therapies have been developed for these common and fatal diseases. One credible explanation is that the primary focuses of investigation, host inflammation and cellular injury, are downstream consequences of an overlooked upstream source: the diverse ecosystems of microbes on and in the human body. Interest in the microbiome has exploded in the past decade due to the advent of culture-independent methods of identifying microbes.[2,3] Although a wealth of clinical and experimental evidence suggests that the microbiome is central to the pathogenesis of critical illness, the common diseases of critical illness have been included in surprisingly few modern microbiome studies. In turn, review articles and clinical guidelines on critical illness

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Declaration of interests

I declare no competing interests.

largely ignore the microbiome, neglecting what is, effectively, a 1·5 kg organ containing more DNA than every host organ combined.

Critical illness and the interventions of intensive care substantially alter the microbiome. In turn, the microbiome predicts patients' susceptibility to disease, and manipulation of the microbiome has prevented or modulated critical illness in animal models and clinical trials. In this Review, I describe the altered ecosystem of the microbiome in critically ill patients, focusing on the gut and lungs. I discuss the microbiome's role in sepsis, ARDS, pneumonia, and exacerbations of chronic lung disease, and identify important unanswered questions that may now be resolved with the techniques of modern microbiology.

The ecological effects of critical illness

The observation at the heart of this Review—that critical illness alters the ecosystem of the body's microbiota—was first made in a seminal study by Johanson and colleagues[4] in 1969, decades before the dawn of high-throughput sequencing. Exposure to the hospital setting has minimal effect on the bacterial communities of the upper respiratory tract: the oropharynges of healthy hospital workers and minimally ill patients staying in hospital are no more frequently colonised by Gram-negative rods than are those in people with no hospital exposure (figure 1). Rather, the change in microbiota seen in patients staying in hospital depends on the severity of their illness rather than their physical location. Critical illness substantially alters the physiology of the host, which in turn alters the environmental conditions and community structures of resident microbes. This clinical observation illustrates an oft-cited tenet in microbial ecology, "Everything is everywhere, but the environment selects".[5] Decades later, we have an incomplete but growing understanding of how the internal environment of critically ill patients creates selective pressure on the relative growth of its microbiota.

The composition of every community, microbial or otherwise, is determined by the balance of three ecological factors: immigration into the community, elimination of members from the community, and the relative reproduction rates of the community's members. Any change in the microbiome, whether it be chronic or acute, must be attributable to some combination of these three forces. All three are greatly altered in the gut and lung ecosystems of critically ill patients by the pathophysiological effects of critical illness and interventions of intensive care (tables 1, 2).

The primary route of immigration of microbes into the gut microbiome is via the oropharynx, which itself changes strikingly in critical illness. Johanson and colleagues[4,7] noted that in critically ill patients, healthy oral microbiota are displaced by gram-negative aerobes (figure 1), including prominent members of the Proteobacteria phylum. The catabolic starvation state of critical illness results in decreased immigration of food-associated bacteria and decreased nutritional supply for commensal microbes.[6] Well-studied interventions, such as topical oral decontamination, decrease the bacterial burden of the oropharynx and decrease immigration from the source community.[44]

In healthy individuals, the primary means of microbial elimination from the gut microbiome is transit through and from the gastrointestinal tract, which is normally rapid. Via defecation,

a healthy adult expels about 10^{14} bacterial cells per day.[63] In critically ill patients, transit time is substantially slowed by various pathophysiological (glucose and electrolyte disturbances[8,9] and endogenous opioid production) and therapeutic (sedatives, opiates, and systemic catecholamines[21]) factors. In the stomach, which is normally fast to empty and extremely acidic, transit time slows[36] and pH is neutralised by the use of agents to suppress the production of gastric acid.[38,39] Other mechanisms of microbial elimination are impaired in critical illness: bile salt production drops,[17] IgA production is impaired,[31] and the dense mucosal barrier of secreted antimicrobial peptides is lost.[25,26,32] The net effect is reduced elimination of bacteria, especially in the upper gastrointestinal tract, which is transformed into a pH-neutral reservoir that quickly becomes overgrown by Gram-negative bacteria.[64]

Environmental growth conditions of the gut are transformed in critical illness, which affects the relative reproduction rates of community members. Hypoperfusion and reperfusion of the intestinal wall results in intense mucosal inflammation, leading to a cascade of environmental changes. Increased nitrate concentrations[13] and an altered mucosal oxygen gradient[29] favour the growth of microbes in the Proteobacteria phylum, which contains many clinically familiar gram-negative rods, such as *Pseudomonas aeruginosa* and *Escherichia coli*, and some members of the Firmicutes phylum, such as *Staphylococcus aureus* and *Enterococcus* spp.[14–16] Importantly, in many critically ill patients, the dense intestinal mucus layer is thinned, disrupted, or absent.[25,26] This crucial anatomical component of gut anatomy harbours its own protective microbiota and provides a physical barrier between the intestinal ecosystem and the host. Almost every common clinical intervention used in intensive care (eg, enteral feeding,[43] proton-pump inhibitors,[38,39] systemic catecholamines,[22,23] and systemic antibiotics[65,66]) changes environmental growth conditions for intestinal bacteria (table 1).

The net effect of these alterations in ecology is an unstable and often collapsed community with catastrophically low diversity. The stomach and proximal small intestine, which are usually sparsely populated, become overgrown by a small number of species, such as *E coli*, *P aeruginosa*, and *Enterococcus* spp.[67,68] The upper gastrointestinal tract becomes a stagnant reservoir of potential pathogens, the presence of which is predictive of extra-abdominal infections and multiorgan failure.[64,67] The lower gastrointestinal tract, which in healthy people contains hundreds of distinct bacterial species, loses diversity, and the community is overrun by a few (in some cases only one) bacterial species.[20,69,70] Dominant species include *S aureus*, *Enterococcus* spp, and members of the *Enterobacteriaceae* family (including *E coli* and *Klebsiella* spp). *P aeruginosa*, which is normally low in abundance, grows in prominence.[20,69,71] Additionally, normally rare fungi, such as *Candida* spp, bloom and thrive;[20] culture-based detection of candidaemia is a marker of disease severity and predictive of a poor outcome.[72] Viruses, archaea, and eukaryotes comprise less than 10% of the gut community in healthy individuals,[73] and the effects of critical illness on abundance and behaviour of these organisms are unknown. This catastrophic drop in bacterial diversity, compared with the relatively subtle differences seen across chronic disease states, is astounding. In critical illness the gut microbiome resembles an infection rather than a community.

The absence of specific bacteria in the gut is just as important as the presence of others. The resident microbes of the lower gastrointestinal tract normally serve essential metabolic and immunomodulatory functions. Even slight differences in the abundance of healthy gut bacteria have been implicated in diverse systemic diseases.[74] The lower gastrointestinal tract in critically ill patients becomes an inhospitable desert for these stabilising resident microbes. For example, butyrate is the primary energy source for the epithelial cells that line the colon. Without butyrate these cells are starved and shrivel and degrade.[75] Butyrate also dampens the intestinal and systemic immune response by stimulating the development of regulatory T cells.[76] In studies of the gut microbiome in critically ill patients, butyrate-producing bacteria are uncommon or absent,[20,69–71] and butyrate production is at a minimum.[71] The pathophysiological consequences of this condition are predictable (epithelial cell death and dysregulated inflammation), but the clinical consequences are unknown.

The ecological effects of critical illness are similarly extreme in the respiratory tract (table 2). Although even healthy lungs are subject to constant immigration from oropharyngeal microbes via microaspiration,[77–79] this immigration is accelerated due to depressed consciousness and endotracheal intubation. The dynamics of the aerodigestive tract become inverted during critical illness: whereas in health, the oropharynx is the primary source community for the lungs and the stomach,[80] the overgrown microbial reservoir of the stomach and small intestine becomes the primary source community for the mouth and lungs.[64,67] The oropharynx is usually populated by benign *Prevotella* spp and *Veillonella* spp,[2,77,78] but becomes overrun by potentially pathogenic bacteria, including prominent Proteobacteria, such as *P aeruginosa* and *K pneumoniae*.[4,7,81]

Although elimination of microbes from the respiratory tract is accelerated in critical illness partly by the activation of immune defences, most pathophysiological and clinical factors decrease the rate of microbial elimination. Depressed consciousness and sedation blunt the cough reflex,[46] and endotracheal intubation and acute illness impair the mucociliary escalator.[47] Elevation of the head of the bed decreases the immigration rate of gastric microbiota,[58] but it also impedes microbial elimination, which is predominantly gravity-dependent when cough and mucociliary clearance are impaired.[59] The inactivation of alveolar surfactant decreases the elimination of surfactant-sensitive bacteria.[55,57]

Finally, as discussed in detail below, acute illness substantially changes the environmental growth conditions of the lungs. The normally nutrient-poor environment of the alveolus is flooded with nutrient-rich oedema,[55] pockets of oxygen and heterogeneous temperature gradients are established,[48,49] and the signalling molecules of the host stress response selectively promote the growth of potential pathogens.[23,50,51] The ubiquitous use of systemic antibiotics further alters the relative reproduction rates of community members. The predicted effect of these ecological forces in the lungs, therefore, is a state of increased immigration, decreased elimination, and favourable growth conditions for potential pathogens.[61,82–84] Understanding of these ecological forces will be informed by longitudinal, culture-independent surveys of microbial com munities in the upper and lower respiratory tracts in critically ill patients.

Gut-derived sepsis: the inarguable and the unknown

The suspicion that the intestinal microbiome can be turned against the host is as old as germ theory. In 1868, contemporaneous with Pasteur, Herman Senator speculated that "self-infection" within the gastrointestinal tract could release systemic factors that cause fever, tachycardia, and obtundation.[85] In 1952, a decade after the introduction of penicillin,[86] Fine and colleagues[87] reported that pretreating the gut with enteric antibiotics significantly lessened the risk of death in an animal model of haemorrhagic shock. In 1972, 5 years after the first description of ARDS,[88] Cuevas and colleagues[89] showed that the disease could be prevented in animal models of shock by pretreatment with enteric antibiotics.

During severe systemic illness, such as sepsis or haemorrhagic shock, the bacterial content of the gut determines the severity of systemic injury (figure 2). When the bacterial burden of the gut is minimised, either by pretreatment with enteric antibiotics or by use of germ-free animals, the inflammation and injury sustained by distal organs in shock is lessened. This relation has been reported consistently across species (mice,[90,93] rats,[94] rabbits,[89] and dogs[87]), types of shock (haemorrhage,[87] sepsis,[89] and ischaemia–reperfusion[90]), and decades of rigorous inquiry. The microbiome, therefore, is of clear relevance to any discussion of precision medicine in critical care: the treatment groups in these studies differed not in genetics or exposure history but rather only in their microbiota (figure 2).

In the 1980s, these experimental observations prompted clinical investigation of the suppression of gut bacteria in patients at risk of critical illness. Selective decontamin ation of the digestive tract (SDD) is achieved by prophylactic administration of antibiotics tailored to keep overgrowth of potential pathogens in the gut to a minimum. Since the first (which was also the first positive) randomised controlled trial in 1987,[95] SDD has been tested in more than 65 randomised controlled trials studying more than 15000 patients.[96] The findings are unambiguous: patients who receive SDD are less likely to develop multiorgan failure[91] or die[96] than patients who do not (figure 2). Nevertheless, clinical use of SDD remains uncommon, especially in North America, due to perceived risk of antimicrobial resistance, although this concern is not supported by large clinical trials and meta-analyses.[97] Although the ecological effects of SDD on antibiotic-resistant pathogens at the intensive-care-unit level remain controversial,[98] the reality of the patient-level benefits are beyond debate.

This connection between patients' microbiota and their susceptibility to critical illness has been reinforced by an even broader scope of study. When more than 10000 hospital inpatients were stratified according to estimated degrees of intestinal dysbiosis, a strong and consistent dose–response relation was uncovered between disorder of the microbiome and subsequent development of severe sepsis.[99] This association between the microbiome and susceptibility to critical illness has, therefore, been shown at every level of inquiry: the laboratory bench, clinical trials, meta-analyses, and population studies. Yet, despite the clarity of this biological signal, the mechanisms behind it remain controversial and incompletely understood.

The oldest, most intuitive explanation for so-called gut-derived sepsis is that in states of critical illness, bacteria and bacterial products escape from the gut and translocate via the

bloodstream to distal organs, where they provoke inflammation and injury. The intestinal wall of critically ill patients is permeable, and the degree of permeability correlates with subsequent risks of organ injury and death.[100] However, in a study of trauma patients at high risk of multiorgan failure,[101] serial blood cultures drawn from indwelling portal vein catheters have shown minimum evidence of bacterial translocation and no association between portal vein bacteraemia and subsequent illness. The explanation of bacterial translocation, at least via a blood-borne route, therefore, waned in popularity. The explanation was subsequently refined after consideration of intestinal anatomy.[12] The lower gastrointestinal tract drains not only into the portal circulation but also into mesenteric lymph nodes. These nodes drain to the thoracic duct, which in turn empties into the left subclavian vein. Therefore, the lungs are the first capillary bed in the body to filter the 1–4 L chyle per day that is emptied into the blood via the thoracic duct. These anatomical considerations gave rise to the so-called gut-lymph hypothesis.[12]

Substantial clinical and experimental evidence supports the gut-lymph hypothesis. In clinical studies of critically ill high-risk surgical patients and in animal studies of shock, bacteria have been cultured from the mesenteric lymph nodes.[10,12,102] Furthermore, detection of bacteria in mesenteric lymph is predictive of subsequent sepsis and infectious complications.[10,103] In animal studies of shock, ligation of the mesenteric duct protected against lung injury,[102] and the harvested mesenteric lymph of critically ill animals can provoke lung injury in otherwise healthy animals.[104] Of note, the toxicity of this lymph does not depend on the presence of endotoxin or of detectable bacteria,[104] which suggests that other bacterial or tissue injury factors are important mediators of injury.

A final explanation for gut-derived sepsis posits that translocation of microbes and microbial products is not necessary for the microbiome to cause systemic inflammation and injury.[22,105,106] Just as the community composition of the gut microbiome is altered by the intestinal environment in critically ill patients, the behaviour and virulence of individual community members are also changed.[22] A bacterial strain that is normally inert and invisible to the host immune system can be transformed by the conditions of critical illness, gaining virulence that ignites systemic inflammation and sepsis. The virulence of pathogens familiar in intensive care is promoted by conditions of nutrient scarcity, competition from neighbouring community members, disruption of stabilising commensal relationships,[20] and exposure to the mediators of the host stress response (eg, catecholamines, inflammatory cytokines, and endogenous opioids[39,47,48]).

In all likelihood, the pathogenesis of gut-derived sepsis, like most processes in critical illness, is multifactorial, replete with biological redundancy.[106,107] All three hypotheses (systemic translocation, gut-lymph translocation, and in-situ virulence) probably explain complementary features of a complex pathogenesis of multiorgan failure, and all three will be informed by the revolution in culture-independent microbiology. The detection and identification of translocated bacteria and characterisation of collapsing gut communities are no longer limited by insensitive culture-based techniques, which cannot detect most gut bacteria.[108] Modern techniques will also inform understanding of how clinical interventions contribute to these parallel processes. Many daily therapies and interventions in intensive care increase intestinal permeability (eg, nonsteroidal anti-inflammatory drugs[109] and

parenteral feeding[55,82]), bacterial translocation (eg, antibiotics,[65] corticosteroids,[110] and opiates[111]), and bacterial virulence (eg, opiates[19] and catecholamines[22,51]). With modern techniques, the mechanisms behind the microbiome's role in the progression from acute injury to systemic inflammation to multiorgan failure to death can finally be unfolded.

The radically altered ecology of the injured alveolus

Even in healthy individuals the lungs are subject to constant bombardment by bacteria from the upper respiratory tract.[77–80] Unlike the gut, however, the alveolar space is an ecologically unfavourable environment for most bacteria and reproduction is minimal.[77,112] An important reason for low reproduction is the lack of nutrient substrate for bacterial metabolism. Whereas the gut lumen offers an abundance of protein and carbohydrate energy sources, the alveolus is empty except for the thin bactericidal layer of lipid-rich surfactant that lines the epithelium. From the perspective of bacteria, healthy alveoli are inhospitable. In states of alveolar injury, however, such as in ARDS or pneumonia, the environmental conditions shift abruptly (figure 3). The previously empty alveoli are flooded with protein-rich fluid, providing a newly abundant energy source for reproducing microbes. The bactericidal surfactant layer is inactivated[55,57] and microbial elimination is slowed by impairment of mucociliary clearance.[47] Ecologically, the injured alveoli begin to resemble the gut more than healthy lungs and, therefore, it is unsurprising that most pathogens that arise in critical illness are of enteric origin. The microbiome and alveolar injury can propel each other in a dysregulated feedback loop that spans the host–microbiome divide (figure 3).[55,113]

Important features of the relation between alveolar injury and lung microbiota have been validated by innovative animal studies.[56] Sterile direct lung injury in mice leads to increases in the bacterial content of the lungs, indicating increased reproduction. The lung community membership shifts towards overgrowth of specific community members that were present in small numbers before injury. Lavage fluid from injured lungs contains the specific nutrients that are metabolised by the newly enriched species, as predicted by the hypothesis that lung injury alters the microbiome via changes in nutrient availability. Finally, when the bacterial communities from injured lungs are introduced into the lungs of otherwise healthy mice, they provoke more inflammation and injury than do bacteria acquired from uninjured lungs. These novel findings reveal numerous new targets for clinical intervention. Virtually all preventive and therapeutic strategies for ARDS have been aimed at blunting host inflammation and injury. This model suggests that the dynamic interface between the host and its disordered lung communities (figure 3) is a ripe, unexplored target for intervention.

This model of pathogenesis can apply to ARDS and to pneumonia, and might explain why such extensive clinical overlap exists between the two disorders. Pneumonia is the most common cause of ARDS,[114] and roughly half of patients with established ARDS develop pneumonia during intensive care.[114,115] In the most convincing study so far to test the preventive value of lung-protective ventilation in patients without ARDS, the intraoperative use of larger tidal volumes (which induce alveolar injury and leak,[60] figure 3) increased the rate of postoperative pneumonia by a factor of five (from 1·5% to 8·0%).[116]

Nutrient supply is not the only way the ecology of the alveolus changes in critically ill patients. The influx of oedema creates steep oxygen gradients, which shape bacterial community structure.[29,48] Surfactant is inactivated, which disinhibits the growth of sensitive bacteria,[55,57] and mucociliary clearance is impaired.[47] The cells of innate immunity (macrophages and neutrophils) increase in number and activation, which causes the alveolar concentration of molecules related to the host stress response to increase.[117]

These molecular stress signals—increased concentrations of catecholamines and inflammatory cytokines—affect lung bacteria.[118,119] In vitro, the growth of *P aeruginosa* is increased by the presence of catecholamines (figure 4).[51] In human bronchoalveolar lavage samples, increased alveolar catecholamine concentrations correlate strongly with collapse of the lung microbiome around one dominant species (most frequently *P aeruginosa*, figure 4).[50] Thus any source of alveolar injury and inflammation, whether direct (eg, aspiration or ventilator-induced lung injury[60]) or indirect (eg, sepsis or shock) can trigger a cascade of inflammation leading to increased concentrations of intra-alveolar catechol amines,[120] which in turn promote the growth and virulence of select bacterial community members and a disordered bacterial community that perpetuates alveolar inflammation (figure 4). Bacterial growth promotion by host stress molecules is not unique to *P aeruginosa*, and is also seen with *Streptococcus pneumoniae*,[121] *S aureus*,[122] and *Klebsiella pneumoniae*.[123] Additionally, as well as catecholamines, growth promotion is seen with TNFα, interleukins 1, 6, and 8, and glucocorticoids.[23,24,124,125] The web of interactions between the lung microbiome and alveolar inflammation is complex, dynamic, and bidirectional.

Exacerbations of chronic lung disease are not acute bacterial infections

Not all respiratory failure in intensive care is attributable to alveolar injury. A common presentation is the clinical exacerbation of chronic airway diseases, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis. These exacerbations are associated with increased and persistent airway inflammation, and result in severe morbidity and death and high expense related to intensive care.[126]

Although viral infections have an unambiguous role as a common precipitant of exacerbations, the role of bacteria in the pathogenesis of exacerbations has been controversial for decades.[126] The theory that exacerbations represent acute bacterial infections ranges from universally assumed (cystic fibrosis[127] and bronchiectasis[128]) to highly controversial (COPD[53]) to widely dismissed (asthma[129]). Confusion and debate on this issue stems from the poor sensitivity of culture-based approaches in the characterisation of lung communities.[2,126] Culture-independent techniques have helped to clarify this long-debated relation between bacteria, infections, and exacerbations.

Ecologically, infections are characterised by an increase in microbial burden and a decrease in community diversity, coupled with increased host inflammation and tissue injury. Bacterial pneumonia, a true lung infection, exemplifies these features: it is characterised by increased bacterial burden and low community diversity (generally one dominant pathogen).[62,83,130] These features correlate tightly with multiple indices of host

inflammation, including alveolar neutrophilia[93] and high alveolar concentrations of catecholamines[50] and TNF-α.[131]

By contrast, exacerbations consistently lack these defining ecological features of infection. Culture-independent studies have compared bacterial communities at baseline and during exacerbations in the airways of patients with COPD,[132,133] cystic fibrosis,[134–138] or bronchiectasis.[139] With remarkable consistency, all studies report no increase in bacterial burden and no decrease in community diversity during exacerbations. By any conventional or modern definition, therefore, exacerbations are not acute bacterial infections of the airways.

Nor do exacerbations behave clinically like true acute respiratory infections, such as pneumonia. Whereas invitro bacterial sensitivity to antibiotics is crucial in the management of pneumonia, there is no detectable relation between antibiotic susceptibility of cultured organisms and clinical response to therapy in exacerbations, even in cystic fibrosis.[140,141] Antibiotics are unquestionably useful in the treatment of pneumonia, but in respiratory exacerbations views on their use range from controversial (COPD) to useless (asthma). Additionally, whereas pneumonia is the most common cause of sepsis, exacerbations rarely or never provoke a septic response.

Although exacerbations are not bacterial infections, the microbiome is clearly involved in the pathogenesis of exacerbations. Baseline differences in airway microbiota are predictive of subsequent exacerbation frequency.[142] The intervention most consistently proven to decrease exacerbation frequency (in COPD,[143] cystic fibrosis[144] and bronchiectasis[145]) is azithromycin, a macrolide antibiotic. In exacerbation states, membership of the lung bacterial community shifts, often towards enrichment of the Proteobacteria phylum,[133,146] which contains clinically relevant Gram-negative rods, such as *Pseudomonas* spp and *Haemophilus* spp. As opposed to infections, therefore, exacerbations are more accurately described as respiratory dysbiosis: disorder of the respiratory ecosystem coupled with a dysregulated host immune response. Airway inflammation leads to altered microbial growth conditions and the resulting disordered bacterial community further drives airway inflammation.[126] This self-perpetuating positive-feedback loop might explain why clinical exacerbations can last weeks longer than the presence of their triggers, and why macrolides (which have antimicrobial and immunomodulatory effects[147]) have such consistently demonstrated preventive benefits across diseases.[143–145]

Important clinical lessons and areas for further study

With virtually every treatment used in intensive care, the patient's microbiota are knowingly or unknowingly manipulated (tables 1, 2). In view of the clear relevance of the microbiome to outcomes in critically ill patients, the ecological effects of interventions must be studied rigorously. In instances in which the effects are known, they should be taken seriously. For instance, proton-pump inhibitors decrease elimination of gastric microbiota[38] and increase immigration of bacteria into the lungs, which increases the risk of pneumonia.[148] Maddeningly, however, proton-pump inhibitors are commonly included in treatment bundles purported to prevent ventilator-associated pneumonia, and are prescribed indiscriminately to

critically ill patients. Other common interventions need to be reconsidered from an ecological perspective. Raising of the head of the patient's bed decreases immigration to the lungs of gastric microbiota compared with supine positioning,[149] but this practice also compromises microbial elimination from the lungs, which is gravitationally dependent in critically ill patients.[59] Lowering the head of the bed might be more protective than raising it,[59] but has not been studied in clinical trials. Historically, the composition of enteral nutrition has been tailored to meet the perceived metabolic needs of the host, without taking into account its effects on the microbiome. This approach, however, might overlook the most direct means of shaping environmental growth conditions within the gut microbiome.[41] Observational human studies alone cannot disentangle the effects of critical illness from the effects of its treatment (eg, antibiotics). Thus future investigation of the microbiome's role in critical illness will require the use of animal studies and prospective, controlled human trials.

The microbiome can be manipulated therapeutically, as has been shown by the success of faecal microbiota transplantation in the treatment of refractory *Clostridium difficile* infection. Evidence of therapeutic manipulation of the microbiome in critical illness is promising.[106] SDD is the most thoroughly studied intervention in critical care research, and has unambiguous benefits in the prevention of infections, multiorgan failure, and death.[91,96] Early intensive-care studies of probiotics suggest that they decrease the risk of pneumonia and shorten the length of stay in the intensive-care unit for ventilated patients[150] and decrease systemic infections in high-risk postoperative patients.[151] Improved survival has been reported in a mouse model of sepsis.[152] These blunt and broad interventions, with one-size-fits-all cocktails of antibiotics or probiotics, however, represent the opposite of targeted therapy. With the advent of culture-independent microbiology, the means are at last available to identify specific features of the microbiome that promote and disrupt homoeostasis in critically ill patients. At the current pace of development, point-of-care community sequencing and identification of pathogens will be available and affordable within years rather than decades.[62,144] Improved understanding of what constitutes a healthy microbiome is urgently needed in this population so that rational therapies to restore and maintain it can be developed.

The microbiome is central to the biology of critical illness and, therefore, should be included in any discussion of disease phenotyping in intensive care. Most studies and reviews of precision medicine in critical illness, however, focus on host genetics, immune responses, and exposures.[153–155] None of these accounts for the differences in outcomes attributable solely to differences in patients' microbiota (figure 2). Before tailored therapy can be provided to patients, how the microbiota informs prognosis and response to treatment needs to be understood. All clinical trials in critical illness should consider assessment of the microbiome, in the gut and the lungs, as an important secondary outcome, as both a mediator of disease and as a modifier of therapy.

Neonates represent an important and understudied population as they are highly vulnerable to alterations in the developing microbiome and to life-threatening critical illnesses. Premature neonates are subjected to innumerable microbiome-altering exposures (eg, antibiotics and formula feeding) and lack mature innate and adaptive immune responses. In

multiple studies, the composition of the early gut microbiome has been predictive of neonatal sepsis,[70,156,157] which can be plausibly explained by either enteric harbouring of potential pathogens or systemic immune derangements provoked by intestinal dysbiosis. Experimental data suggest that early exposure to a diverse intestinal microbiome is essential for the development of an intact immune response: newborn mice with antibiotic-suppressed microbiota have increased susceptibility to pulmonary infections[158] and bacterial sepsis.[159] Necrotising enterocolitis, a devastating and idiopathic disease of neonates, has been linked to intestinal dysbiosis in animal[160] and human studies,[161] and randomised controlled trials support a protective role of probiotics.[162,163] The acute and chronic consequences of dysbiosis in neonates are worthy of immediate clinical and experimental study.

Finally, although this Review has focused on the causes and consequences of acute perturbations of the microbiome in critical illness, the research into intensive-care outcomes in the past decade has convincingly shown that the sequelae of critical illness persist long after patients are extubated and discharged. Survivors of ARDS and sepsis have chronic deficits in cognitive function and functional status, and are at high risk of re-admission in the months after discharge,[164] disproportionately so for infection-related events. The mechanisms underlying this so-called postintensive-care syndrome are poorly understood, but the contribution of a persistently altered microbiome should be explored. Derangements of the microbiome persist for weeks and months after even a short antibiotic course,[66] and how quickly or completely the microbiome recovers after the insults and disruptions of critical illness are unknown. Research is needed to define the natural history of microbiome recovery after critical illness, to determine whether recovery can be accelerated (eg, via probiotics or faecal microbiota transplantation), and whether this recovery improves long-term outcomes for patients. In patients recovering from multiorgan failure, it may be that microbiome is the last organ to recover.

Conclusions

Although the importance of the microbiome in critical illness has been established for a half century, the revolution in culture-independent microbiology has at last yielded tools capable of determining its contribution to the pathogenesis of sepsis, ARDS, and multiorgan failure. Continuing clinical and experimental trials will explore how the microbiome is altered in disease, and in turn how its disturbance perpetuates organ injury. The microbiome represents a key therapeutic target for the prevention and treatment of critical illness, and should be included in any discussion of precision medicine in the intensive care unit.

Acknowledgments

I am supported by the National Institutes for Health (UL1TR000433) via a grant provided by the Michigan Institute for Clinical & Health Research, the Host Microbiome Initiative of the University of Michigan, and the University of Michigan Center for Integrative Research in Critical Care. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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Search strategy and selection criteria

I searched MEDLINE and Web of Science without date or language restrictions, with the initial search terms of "([microbiota] OR [flora]) AND ([sepsis] OR [shock] OR [acute respiratory distress syndrome] OR [multiorgan failure])."

I manually screened titles and abstracts to exclude unrelated studies. I read all relevant articles, and identified additional relevant articles via citations. Due to space limitations, only references with immediate relevance to topics discussed in the Review are included.

Key messages

- The microbial ecosystems of the gut and the lungs change substantially in critically ill patients, resulting in dramatic changes to bacterial communities
- In animal studies of shock, the microbial contents of the gut determine the severity of multiorgan failure and the risk of death, an observation supported by trials of selective manipulation of the gut microbiome in human beings
- The mechanisms that drive gut-derived sepsis are incompletely understood and multifactorial, offering numerous unexplored therapeutic targets
- During lung injury, the bacterial ecosystem of the alveolus shifts to a state of abundance in nutrients and growth-promoting host stress signals, leading to a positive feedback loop of inflammation and dysbiosis
- The microbiome is a key therapeutic target for the prevention and treatment of critical illness, and it should be included in any discussion of precision medicine in the intensive care unit

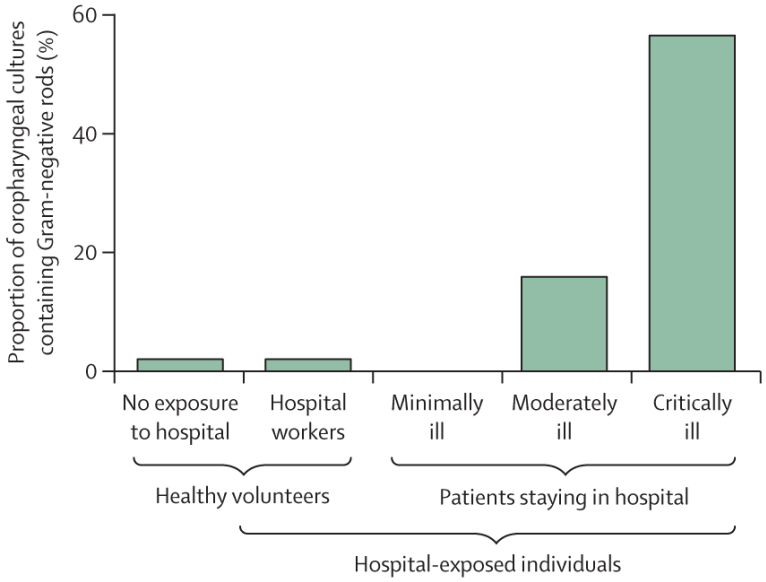

Figure 1. The altered ecosystem of the critically ill patient

Changes in microbiota depend upon severity of illness rather than physical location and bacterial exposure.[4]

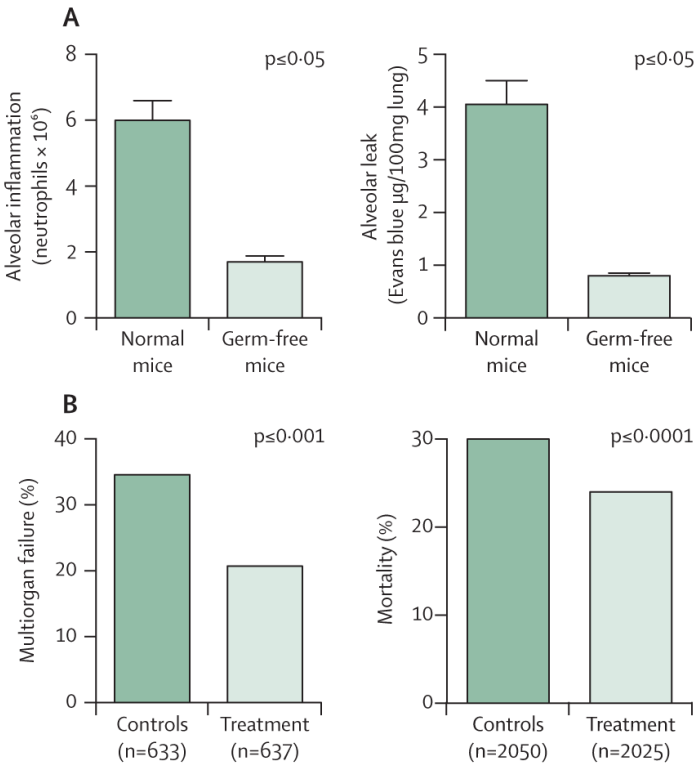

Figure 2. Manipulation of the microbiome and the prevention of critical illness

(A) In diverse models of shock, germ-free mice are protected from the alveolar inflammation and injury seen in acute respiratory distress syndrome.[90] (B) In clinical trials, manipulation of gut microbiota with antibiotics (selective decontamination of the digestive tract) protects against extra-abdominal infections, multiorgan failure, and death.[91,92] Part A was adapted from reference 90 by permission of the American Association of Immunologists.

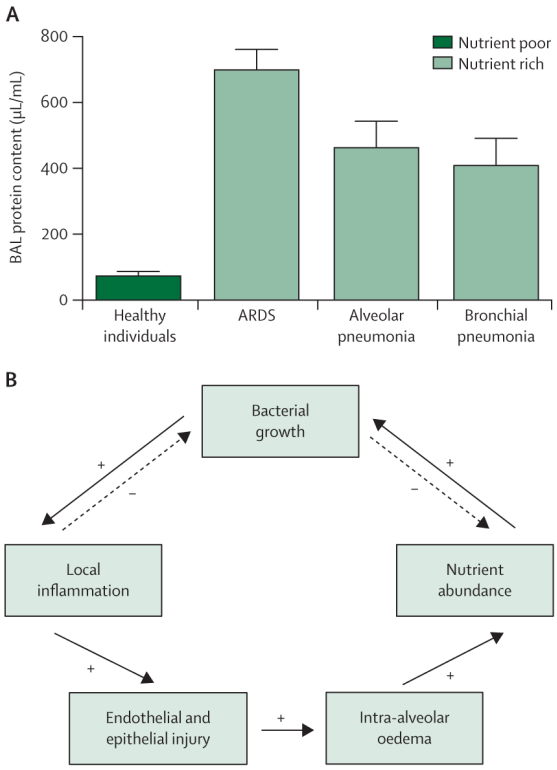

Figure 3. Alteration of bacterial ecology in injured alveoli

(A) Unlike in the healthy gut, the environment in healthy lungs is nutrient poor for bacteria and the protein content of alveolar lavage fluid is at a minimum. (B) In states of health, bacterial growth in the alveolar space is limited by the local inflammatory response it provokes and by its depletion of available nutrients. In conditions of alveolar injury, such as in ARDS and pneumonia, the alveolar space is flooded with nutrient-rich fluid, which promotes bacterial growth that in turn perpetuates a positive-feedback loop of inflammation, injury, alveolar oedema, and further dysbiosis. BAL=bronchoalveolar lavage. ARDS=acute respiratory distress syndrome. Part B was reproduced from reference 113 by permission of Elsevier.

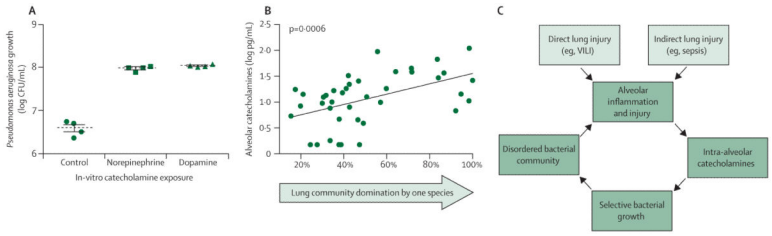

Figure 4. Catecholamines and disorder in the alveolar bacterial ecosystem

(A) The growth of bacteria, such as *Pseudomonas aeruginosa*, is promoted in vitro by catecholamines, such as norepinephrine and dopamine.[51] (B) In the human lung microbiome, increased catecholamine concentrations are strongly associated with community collapse and the emergence of one dominant species.[50] (C) In states of critical illness, direct and indirect lung injury provoke alveolar inflammation, which promotes catecholamine production and creates a positive-feedback loop of dysbiosis and inflammation.[50] CFU=colony forming unit. VILI=ventilator-induced lung injury. Part A adapted from reference 51 by permission of American College of Chest Physicians. Part B adapted from reference 50 by permission of American Thoracic Society.

Table 1

Ecological effects of critical illness on the gastrointestinal microbiome

	Microbial immigration	Microbial elimination	Environmental growth conditions
Pathophysiological processes			
Decreased oral intake	Decreased immigration of food-associated microbiota[6]	No direct effect	Shift to stress conditions of nutrient scarcity and altered nutritional substrate[6]
Altered oropharyngeal microbiota	Increased immigration of Proteobacteria and potential pathogens[4,7]	No direct effect	No direct effect
Intestinal dysmotility	No direct effect	Decreased elimination, increased upper-gastrointestinal community burden	No direct effect
Systemic hyperglycaemia and electrolyte disturbances	No direct effect	Decreased elimination (intestinal dysmotility)[8,9]	No direct effect
Gut hypoperfusion, reperfusion injury, impaired mucosal integrity	No direct effect	Increased elimination via translocation to mesenteric lymphatics[10–12]	Increased mucosal inflammation, increased free radical concentrations and nitrate availability;[13] shift from commensal anaerobes to Proteobacteria and select Firmicutes[14–16]
Decreased bile salt concentration[17]	No direct effect	Decreased elimination of bile-sensitive species (eg, *Enterococcus* spp)[18]	Selective overgrowth of bile-sensitive species (eg, *Enterococcus* spp)[18]
Endogenous opioid production	No direct effect	Decreased elimination (intestinal dysmotility)	Selective increase in virulence of opioid-responsive species (eg, *Pseudomonas aeruginosa*),[19] disruption of stabilising commensal relationships[19,20]
Endogenous catecholamine and inflammatory cytokine production	No direct effect	Decreased elimination (intestinal dysmotility)[21]	Selective promotion of growth and virulence of potential pathogens (eg, *Pseudomona. aeruginosa*),[22–24] increased mucosal inflammation (via splanchnic hypoperfusion), decreased oxygen tension and pH
Disruption of intestinal mucus layer[25,26]	No direct effect	Increased elimination via translocation to mesenteric lymphatics[27,28]	Altered nutrient supply, altered oxygen gradients,[29] loss of mucus reservoir of antibacterial peptides[30]
Impaired mucosal immunity: decreased IgA and defensin production[31,32]	No direct effect	Decreased elimination of potential pathogens, increased elimination via translocation to mesenteric lymphatics[33]	Loss of growth inhibition for potential pathogens, decreased abundance of commensal Bacteroidetes[34,35]
Clinical interventions			
Supine positioning	No direct effect	Decreased elimination from upper gastrointestinal tract (intestinal dysmotility)[36,37]	No direct effect
Gastric-acid suppression	No direct effect	Decreased elimination from upper gastrointestinal tract (neutralised pH)[38,39]	Selective growth promotion of acid-intolerant bacteria[38,39]
Enteral feeding	No direct effect	Increased elimination due to antimicrobial actions of luminal bile salts,[17] decreased elimination via translocation to mesenteric lymphatics[40]	Altered nutritional substrate,[6,41] shift away from stress conditions of nutrient scarcity

	Microbial immigration	Microbial elimination	Environmental growth conditions
Parenteral feeding	No direct effect	Increased elimination via translocation to mesenteric lymphatics[11,42]	Loss of growth inhibition for potential pathogens via impaired mucosal immunity (eg, decreased IgA secretion)[43]
Sedatives, opiates and neuromuscular blockade	No direct effect	Decreased elimination (intestinal dysmotility)	Selective increase in virulence of opioid-responsive species (eg, *Pseudomonas aeruginosa*),[19] disruption of stabilising commensal relationships[19,20]
Systemic catecholamines	No direct effect	Decreased elimination (intestinal dysmotility)[21]	Selective promotion of growth and virulence of potential pathogens (eg, *Pseudomonas aeruginosa*),[22,23] increased mucosal inflammation (via splanchnic hypoperfusion), decreased oxygen tension and pH
Oral decontamination (eg, topical chlorhexadine)	Decreased immigration of oropharyngeal microbiota	No direct effect	No direct effect
Selective decontamination of the digestive tract	Decreased immigration of oropharyngeal microbiota	Increased elimination of select bacteria (eg, *Enterobacteriaceae* spp)[44]	Selective growth suppression of select bacteria (eg, *Enterobacteriaceae* spp)[44]
Systemic antibiotics	No direct effect	Increased elimination of select bacteria (depending on antibiotic regimen)	Selective growth suppression of bacteria (depending on antibiotic regimen)

Table 2

Ecological effects of critical illness on the respiratory microbiome

	Microbial immigration	Microbial elimination	Environmental growth conditions
Pathophysiological processes			
Altered oropharyngeal microbiota	Increased immigration of Proteobacteria and potential pathogens[4,7]	No direct effect	No direct effect
Depressed level of consciousness	Increased immigration via aspiration of oropharyngeal and gastric contents[45]	Decreased elimination (impaired cough reflex)[46]	No direct effect
Aspiration of gastric contents[45]	Increased immigration of gastric microbiota[45]	No direct effect	No direct effect
Impaired mucociliary clearance[47]	No direct effect	Decreased elimination (impaired mucociliary escalator)[47]	No direct effect
Increased bronchial mucus production	No direct effect	No direct effect	Increased nutrient substrate, altered gradients of oxygen[48] and temperature[49]
Endogenous catecholamine and inflammatory cytokine production	No direct effect	Increased elimination via innate and adaptive immune response	Selective promotion of growth and virulence of potential pathogens (eg, *Pseudomonas aeruginosa*)[23,24,50,51]
Recruitment and activation of neutrophils	No direct effect	Increased elimination of select community members[52]	Selective suppression of bacterial growth,[52] increased free radical concentrations and nitrate availability,[13,53] altered temperature gradients[49,54]
Alveolar oedema	No direct effect	No direct effect	Increased and altered nutrient substrate,[55,56] altered oxygen gradient
Inactivation of alveolar surfactant	No direct effect	Decreased elimination of surfactant-sensitive bacteria[55,57]	Loss of growth inhibition for selective potential pathogens[57]
Clinical interventions			
Supine positioning	Increased immigration via aspiration of oropharyngeal and gastric microbiota[58]	No direct effect	No direct effect
Head of bed raised	Decreased immigration via aspiration of oropharyngeal and gastric microbiota[58]	Decreased elimination (gravitationally limited mucus clearance[59])	No direct effect
Endotracheal intubation	Increased immigration via aspiration of oropharyngeal microbiota	Decreased elimination (impaired cough and mucociliary escalator)	Altered airway temperature and humidity
Mechanical ventilation	No direct effect	No direct effect	Increased alveolar oedema;[60] increased neutrophil, cytokine, and catecholamine concentrations[60]
Subglottic suctioning	Decreased immigration of oropharyngeal microbiota[61]	No direct effect	No direct effect
Gastric-acid suppression	Increased immigration of gastric microbiota[38,39]	No direct effect	No direct effect

	Microbial immigration	Microbial elimination	Environmental growth conditions
Sedatives, opiates, and neuromuscular blockade	No direct effect	Decreased elimination via impaired cough reflex and mucociliary clearance	No direct effect
Systemic catecholamines	No direct effect	No direct effect	Selective promotion of growth and virulence of potential pathogens (eg, *Pseudomonas aeruginosa*)[50,51]
Oral decontamination (eg, topical chlorhexadine)	Decreased immigration of oropharyngeal microbiota	No direct effect	No direct effect
Selective decontamination of the digestive tract	Decreased immigration of oropharyngeal microbiota	Increased elimination of select bacteria (eg, *Enterobacteriaceae* spp)[44]	No direct effect
Systemic antibiotics	No direct effect	Increased elimination of select bacteria (depending on antibiotic regimen)	Selective growth suppression of bacteria (depending on antibiotic regimen)[62]