New insights into the gut as the driver of critical illness and organ failure

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Purpose of review
The gut has long been hypothesized to be the 'motor' of multiple organ dysfunction syndrome. This review serves as an update on new data elucidating the role of the gut as the propagator of organ failure in critical illness.

Recent findings
Under basal conditions, the gut absorbs nutrients and serves as a barrier that prevents approximately 40 trillion intraluminal microbes and their products from causing host injury. However, in critical illness, gut integrity is disrupted with hyperpermeability and increased epithelial apoptosis, allowing contamination of extraluminal sites that are ordinarily sterile. These alterations in gut integrity are further exacerbated in the setting of preexisting comorbidities. The normally commensal microflora is also altered in critical illness, with increases in microbial virulence and decreases in diversity, which leads to further pathologic responses within the host.

Summary
All components of the gut are adversely impacted by critical illness. Gut injury can not only propagate local damage, but can also cause distant injury and organ failure. Understanding how the multifaceted components of the gut interact and how these are perturbed in critical illness may play an important role in turning off the 'motor' of multiple organ dysfunction syndrome in the future.

Keywords
apoptosis, critical illness, dysbiosis, gut, permeability

INTRODUCTION

For the past 30 years, the gut has been hypothesized to be the 'motor' of multiple organ dysfunction syndrome [1]. The original theory was straightforward – critical illness induces hyperpermeability, leading to translocation of intact bacteria into the systemic circulation, with subsequent sepsis and organ failure. Although this theory remains attractive in conception and is likely correct in select clinical scenarios, reality is significantly more complex.

The gut is comprised of three interlocking components – the epithelium, the microbiome, and an immune system. The sheer magnitude of these helps underscore the complexity contained within the gut. The surface area of the gut epithelium is half the size of a badminton court [2]. The gut lumen contains approximately 40 trillion bacterial cells, a similar number of cells as the entire host contains [3▪▪]. Finally, the gut contains over 80% of the lymphocytes in the entire host [4]. Despite the enormity of connections within the gut, under basal conditions, all of its components interact with each other to play a crucial role in maintaining host health.

Each component of the gut, however, is markedly perturbed in critical illness. At the bedside, this can be recognized as an ill-defined syndrome called 'gut failure,' where critically ill patients often have a constellation of symptoms, including absent bowel sounds, diarrhea, abdominal distension, vomiting, high tube feeding residuals, gastrointestinal bleeding because of stress ulceration, and intraabdominal hypertension. Although none of these alters prognosis by itself, the presence of three or more of these symptoms on the first day in an ICU stay is associated with a three-fold increase in mortality [5]. Further, elevated intestinal fatty acid-binding

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KEY POINTS

- All elements of the gut – the epithelium, microbiome, and immune system – are markedly dysregulated in critical illness.
- Alterations to the gut induced by critical illness cause organ damage distant from the intestine by a variety of mechanisms.
- Critical illness induces increased gut epithelial apoptosis and hyperpermeability.
- Critical illness induces dysbiosis, wherein the microbiome loses diversity and changes to a more pathogenic flora.

protein (a marker of enterocyte damage) and decreased citrulline (a marker of enterocyte mass) are also associated with mortality in the ICU [6,7▪].

The review will highlight recent advances in the molecular and cellular pathophysiology of the gut in disease that have, in turn, led to a more refined understanding of how the gut can propagate both local and distant organ dysfunction. Of note, it is currently not practical to obtain tissue samples from the gut epithelium or immune system of most critically ill patients, so preclinical studies are generally required to yield many of the new insights described below. It is, however, possible to obtain stool and/or rectal swabs from critically ill patients allowing investigators a new way of studying the gut in critical illness in humans.

THE GUT EPITHELIUM – PROVIDING NOURISHMENT AND ACTING AS THE GREAT WALL OF THE BODY

The human host receives nearly all of its nutrients and is simultaneously protected from trillions of potential microbial invaders by a single cell layer epithelium. At the base of the intestinal crypt, multipotent stem cells actively proliferate and give rise to daughter cells. These cells differentiate as they migrate up the villus to absorptive enterocytes, mucus-producing goblet cells, and enteroendocrine cells. When cells reach the villus tip, they die by apoptosis or are exfoliated whole into the gut lumen. The entire journey from cell birth to migration/differentiation to death occurs in under a week.

The gut provides an enormous absorptive surface area of approximately 32 m^2 [2]. It also provides a semipermeable physical barrier, limiting bacterial and molecular particulate infiltration. Permeability, in turn, is controlled by tight junction proteins between each cell that regulate the paracellular space. All elements of gut integrity are impacted by critical illness. Both sepsis and severe noninfectious inflammation (trauma, burns, hemorrhage, etc.) induce a marked increase in gut epithelial apoptosis with a simultaneous decrease in crypt proliferation [8,9]. This leads to shortened villus length, decreased absorptive capacity, alterations in systemic inflammation, and increased paracellular permeability. Notably, restoration of gut integrity is beneficial in preclinical models of critical illness as intestine-specific overexpression of either the antiapoptotic protein B cell lymphoma 2 (Bcl-2) or the progrowth/prosurvival mediator epidermal growth factor improves survival in murine models of both peritoneal sepsis and pneumonia [10,11].

Critical illness is also associated with intestinal hyperpermeability. Alterations in selected tight junction proteins can be identified as early as 1 h after the onset of murine sepsis, and worsened gut barrier persists for a minimum of 48 h in models of cecal ligation and puncture (CLP; a model of fecal peritonitis), as well as *Pseudomonas aeruginosa* pneumonia [12▪▪]. Sepsis-induced gut hyperpermeability is associated with increased jejunal claudin 2 and junctional adhesion molecule-A expression as well as decreased claudin 5 and occludin expression. Further, colonic tight junctions are also altered in rodent sepsis with increased claudin 2 and alterations in cellular localization of claudins 1, 3, 4, 5, and 8 [13].

Although factors deleterious to the host can exit the gut into the systemic circulation, an alternate route is via the mesenteric lymph [14]. Gut-derived lymph travels directly to the pulmonary circulation and ligating the mesenteric lymph duct prevents lung injury and mortality in burn, trauma, and shock in both large and small animal studies. Highlighting that gut-derived critical illness is not as simple as bacterial translocation, postshock mesenteric lymph in rats subjected to trauma/hemorrhagic shock does not contain any 16S ribosomal RNA genetic material (of bacterial origin), but does contain an increase in damage-associated molecular pattern material [15], suggesting that mesenteric lymph transports proinflammatory mediators that are distinct from bacteria to propagate systemic inflammation.

COMORBID CONDITIONS

As the age of precision medicine is dawning, it has become apparent that patients respond very differently to similar insults. Although some of the differences in host response are assuredly genetically based, others result from a lifetime accumulation of environmental insults and chronic disease states. It is well accepted that preexisting comorbidities are associated with increased mortality in critical illness.

As an example, a dataset of 6.6 million patients from Denmark from 1996 to 2014 demonstrated that alcohol abuse, diabetes mellitus, cardiovascular diagnoses, and cancer are associated with increased mortality following sepsis compared with baseline [16].

Gut integrity is worsened by numerous comorbidities. The presence of preexisting lung cancer prior to the onset of CLP induces a further decrease in crypt proliferative capacity compared with previously healthy animals subjected to the same septic insult, and this is associated with increased mortality [17▪▪]. Similarly, the presence of preexisting pancreatic cancer prior to the onset of *P. aeruginosa* pneumonia induces an increase in gut epithelial apoptosis above and beyond what could be expected from either insult in isolation [18].

Gut integrity is also worsened when mice drink alcohol for 12 weeks prior to sepsis induction via CLP. Alcohol/septic mice have increased gut permeability, epithelial apoptosis, and decreased crypt proliferation and villus length compared with previously healthy septic mice, and this is associated with increased mortality [19]. Notably, when alcohol-fed septic animals are given epidermal growth factor, it improves both intestinal integrity and survival to levels seen in water-fed septic animals. However, its efficacy in sepsis is blunted in the setting of chronic alcohol ingestion, as gut integrity and mortality in alcohol-fed septic mice given epidermal growth factor does not approach that in water-fed septic mice given the same agent [20▪▪].

Aging also impacts gut integrity. Aged septic mice have a disproportionate increase in gut epithelial apoptosis, compared with what could be predicted with either age or sepsis in isolation [21]. The impact of age in targeting gut integrity appears to be complex. For example, 8–10-week-old mice with a conditional, intestine-specific deletion of microsomal triglyceride transfer protein have a complete block in chylomicron assembly with lipid malabsorption. When these young mice are made septic via *P. aeruginosa* pneumonia, they are protected against sepsis-induced increases in gut apoptosis and decreases in proliferation and villus length, and this is associated with improved survival [22]. In contrast, aged (20–24 month) mice of the same genotype have increased gut apoptosis following sepsis with increased Bax/Bcl-2 and Bax/B cell lymphoma extra large ratio, and this is associated with worsened mortality [23].

THE GUT MICROBIOME

The microbiome begins forming its symbiotic relationship with the host starting at birth and continues to evolve throughout life [24]. Although the term microbiome refers to all microorganisms residing within (mouth, lungs, gut) or on (skin) the host, the majority of bacterial species and diversity of the microbiome reside within the gut lumen. Over 1000 different bacterial species make up the gut microbiome, containing over 2 million genes [3▪▪,25]. The majority of gut microbes fall within two phyla: *Firmicutes* and *Bacteroidetes,* and the ratio between these changes over life with a relative increase in the former in the elderly [26▪▪,27].

Under basal conditions, the microbiome plays a crucial role in host health. However, critical illness leads to multiple changes to the microbiome, including loss of diversity and overgrowth of pathogenic bacteria [28▪▪]. These changes are frequently exacerbated by antibiotic usage and by unrelated therapies such as proton pump inhibitors, which impact the microbiome nonetheless. Notably, the transition from a healthy microbiome to a pathobiome occurs within hours of a number of varied insults, including sepsis, trauma, and burns [29]. Although the mechanisms underlying this transition are still being determined, it appears the host environment causes not only a change in the relative abundance of bacterial species present but also an alteration of their virulence factors. For example, when *P. aeruginosa* is injected into the cecum of mice subjected to sham surgery and then harvested and implanted into the peritoneum of uninjured mice, it does not cause any mortality. However, when the same microbe is injected into the cecum of mice subjected to 30% hepatectomy and then harvested and implanted into the peritoneum of uninjured mice, all recipient mice die [30]. This suggests that an alteration in the host environment is sensed by bacteria, which, in turn, alter their virulence factors to become pathogenic.

Given the dysbiosis of the gut microbiome in critical illness, modulating the endogenous flora for therapeutic benefit has drawn significant attention [31▪,32▪▪]. This can be done by either giving or stimulating growth of presumptively beneficial microbes (probiotics, prebiotics, synbiotics) or eliminating presumptively detrimental microbes via selective decontamination of the digestive tract. A newer approach to dysbiosis is transplanting an intact microbiome via fecal microbiota transplantation (FMT). FMT has been proven to be highly successful in the setting of recurrent *Clostridium difficile* colitis [33,34▪]. In addition, FMT has been successful in case reports of critically ill patients with dysbiosis-induced diarrhea not caused by *C. difficile* [35,36]. However, the utility of FMT in critically ill patients has practical limits posed by the need to avoid antibiotic usage, as giving antimicrobial agents to a patient would be expected to

immediately alter the transplanted microbiome. Ultimately, although each of these strategies to target the gut microbiome in critical illness is supported by both a theoretical rationale and varying degrees of evidence, none of these currently represent standard of care worldwide.

IMMUNE SYSTEM

Given the constant exposure of the gut to external microbial antigens, the immune system plays a critical role in maintaining the fragile peace between the beneficial — yet potentially dangerous — microbial world residing within the gut lumen and the rest of the host. It does this through constant sampling of the intestinal lumen, utilizing both innate and adaptive responses.

Neutrophils are recruited to the gut lamina propria and respond quickly in the event of bacterial invasion, engulfing, and eliminating invading pathogens [37]. Sepsis reduces the expression of cell surface adhesion molecules E-selectin and intercellular adhesion molecule 1 in the small intestine in the late, hypoinflammatory phase of sepsis, repressing neutrophil influx. When septic mice are given a sirtuin protein 1 (SIRT1) inhibitor, they have increased endothelial expression of these adhesion molecules, as well as increased expression of P-selectin glycoprotein ligand 1 (a ligand of E-selectin) on neutrophils [38]. Notably, this is associated with improved survival, even when mice receive a SIRT1 inhibitor 24 h after CLP, suggesting that sustained neutrophil influx to the intestine may play a role in sepsis mortality.

After bacteria either translocate spontaneously or are taken up from the gut lumen by antigen presenting cells, they are shuttled to the mesenteric lymph node. Antigens are then presented and bacterial-specific IgA is generated against these bacteria [39].

In addition, beyond interacting with the microflora, intestinal intraepithelial lymphocytes are tasked with maintenance of the gut epithelium, especially in response to inflammation. γδ T cells work to help clear infection by having both innate and adaptive immune cell functions. Although much of their function has yet to be elucidated, γδ T cells have been shown to be involved in intestinal mucosal reparation by regulating mucin expression and promoting goblet cell function in the small intestine [40]. Notably, depletion of γδ T cells worsens mortality following CLP [41] whereas septic patients have a lower percentage of circulating γδ T cells compared with healthy controls [42].

In addition to playing a vital role in interacting with the microbiome, the immune system also interacts with the gut epithelium. As sepsis progresses, patients have a marked upregulation of T-cell coinhibitory markers [43]. Blockade of the T-cell coinhibitory molecule PD-1 and its ligand programmed death-ligand 1 (PD-L1) results in restoration of immune functionality across several cell lines and improves survival in multiple models of sepsis [44]. Notably, PD-L1 is also upregulated in the gut epithelium following CLP and septic PD-L1$^{-/-}$ mice have decreased intestinal permeability compared with WT mice [45▪▪].

CROSSTALK BETWEEN GUT AND OTHER DISTANT ORGANS

As the motor of multiple organ dysfunction syndrome, the gut can initiate and propagate injury distant from the intestine. The intestinal epithelium and pulmonary epithelium both are exposed to high concentrations of external antigens and thus, are centers in the initiation and maintenance of the inflammatory response. Notably, crosstalk exists in a bilateral fashion between the gut and the lung. *Staphylococcus aureus* pneumonia in the setting of surfactant protein knockout results in increased gut epithelial apoptosis, increased Bax/Bcl-2 expression and gut levels of tumor necrosis factor and interleukin-1β [46▪]. Gut-derived factors also travel from the intestine via the mesenteric lymph to cause acute respiratory distress syndrome, and ligation of the mesenteric lymph duct in the setting of critical illness prevents distant lung injury. Further, removal of toxic lymph from an injured animal can induce lung injury in a previously healthy animal [14]. The gut microbiome can also influence lung pathophysiology. During pneumococcal pneumonia, there is worsened bacterial dissemination, inflammation, organ damage, and mortality in mice depleted of the gut microbiota. However, FMT normalizes pulmonary bacterial counts and cytokines after pneumococcal pneumonia [47▪▪].

The liver is the organ in closest contact with the gut and is exposed to significant amounts of bacterial components and their metabolites via the portal circulation. There is emerging evidence that the microbiome is associated with acute and chronic liver diseases and that treating dysbiosis by prebiotics, probiotics, and antibiotics can effectively treat numerous complications of severe liver disease seen in critically ill patients such as hepatic encephalopathy [48].

Critically ill patients frequently have acute kidney injury as a result of inflammation and hypoperfusion. Higher permeability of the mesenteric vascular bed directly causes intestinal tissue edema and gut barrier dysfunction, which, in turn, leads to a systemic inflammatory response which worsens

acute kidney injury. Notably short-chain fatty acids produced by the microbiome improve kidney injury induced by ischemia reperfusion by modulating the inflammatory process and ameliorating the effects of hypoxia by improving mitochondrial biogenesis [49]. Further, microbiome products such as glycation end products, phenols, and indoles can accumulate in the setting of kidney injury and lead to further progression of renal damage [50].

Finally, emerging data suggest that the gut microbiome affects the central nervous system via a gut–brain axis, which influences anxiety, depression, cognition, and visceral pain [51▪]. As acute brain dysfunction such as delirium is unfortunately prevalent in critically ill patients and is associated with worse outcomes, the microbiome represents a new target aimed at reversing this common organ dysfunction seen in the intensive care unit.

CONCLUSION

The gut is a highly complex system that under basal conditions maintains tight integration between its epithelium, microbiome, and immune system to benefit host health in a myriad of ways. Unfortunately, all elements of the gut are dysregulated in critical illness, which can both drive and propagate distant organ dysfunction. Therapies aimed at restoring gut integrity, optimizing an effective immune response and reversing the pathological effects of dysbiosis represent exciting avenues of discovery and potential therapeutics for critically ill patients in the future.

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Conflicts of interest

There are no conflicts of interest.

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