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The Gut as the Motor of Multiple Organ Dysfunction in Critical Illness

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Synopsis

All elements of the gut – the epithelium, the immune system, and the microbiome – are impacted by critical illness and can, in turn, propagate a pathologic host response leading to multiple organ dysfunction syndrome. Preclinical studies have demonstrated that this can occur by release of toxic gut-derived substances into the mesenteric lymph where they can cause distant damage. Further, intestinal integrity is compromised in critical illness with increases in apoptosis and permeability. There is also increasing recognition that microbes alter their behavior and can become virulent based upon host environmental cues. Gut failure is common in critically ill patients; however, therapeutics targeting the gut have proven to be challenging to implement at the bedside. Numerous strategies to manipulate the microbiome have recently been used with varying success in the ICU.

Keywords

Sepsis; MODS; Gut; Intestine; Critical Illness

OVERVIEW

The gut has been hypothesized to be the motor of multiple organ dysfunction syndrome (MODS) for the past quarter century (1–3). Whereas initial theories of gut and critical illness suggested that hyperpermeability resulted in bacterial translocation into the systemic circulation, the reality is significantly more complex than was originally hypothesized. All elements of the gut – the epithelium, the immune system, and the microbiome – are impacted by critical illness and can, in turn, propagate a pathologic host response. Further, alterations in the gut can lead to both local and distant insults, via alterations in homeostatic processes and defense mechanisms as well as release of toxic mediators into both mesenteric lymph and the systemic circulation. Although considerable effort has been put into directly targeting the gut for therapeutic gain in critical illness, the results to date have been modest. This review will focus on both the cellular and molecular underpinnings of how the gut

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functions as the motors of MODS as well as clinical ways in which the gut can, at least in part, be potentially manipulated for therapeutic gain.

THE GUT IN HEALTH

Epithelium

The gut contains a single layered epithelium with a myriad of important functions. It provides a large surface area – estimated to be around ~32m^2 or half the size of a badminton court (4) -- for use in nutrient absorption and preventing entrance of pathogens from its lumen. Microscopically, the gut is in a state of constant renewal from the multipotent stem cells near the crypt base. These give rise to daughter cells which then give rise to four major intestinal cell types: a) enterocytes which absorb nutrients and make up >90% of intestinal epithelial cells, b) mucus-producing goblet cells, c) hormone-producing enteroendocrine cells, and d) defensin-producing Paneth cells that protect intestinal stems cells and play a role in intestine-microbiota interactions (5). Unlike other cells in the gut which migrate upwards along the villus, Paneth cells migrate downwards towards the crypt base. The journey from cell birth, differentiation and migration along the villus to cell loss via either apoptosis or luminal sloughing of intact cells takes only 5–7 days in a healthy human.

Immune System

The intestine is the largest lymphoid organ of the body (6). It contains four immune cell compartments: Peyer's patches, the lamina propria, mesenteric lymph nodes and intraepithelial lymphocytes. Peyer's patches come in contact with luminal antigens and direct antigen-presenting cells to the mesenteric lymph nodes. This sets off the immune differentiation of T and B cells in the draining nodes. The highly complicated gut mucosal immune system plays a myriad of roles in host defense including (but not limited to) antigen recognition, presentation, amplification of antigen-specific response, and production of cytokines and chemokines (7).

Microbiome

There are ten times more bacterial cells in a human than host cells -- 100 trillion bacteria to 10 trillion human cells (8). Under normal conditions, there is a well tolerated symbiotic relationship between the human host and its microbiome, which has a robust diversity, with the predominant species being *Bacteroides* and *Firmicutes*. With the recent explosion in our (still nascent) understanding of the microbiome, it has become apparent that the diversity of an individual’s microbiota is dependent on a wide variety of factors starting from the type of birth they underwent (vaginal or Cesarean section) to the diet they eat to their age to even the pets they have (9).

PRECLINICAL INSIGHTS INTO THE ROLE OF THE GUT AS THE MOTOR OF MODS

The gut lymph hypothesis

Given the overwhelming number of bacteria that reside in the intestine, the initial hypothesis for why the gut is the motor of MODS was whole bacteria translocation that spread via

portal circulation. While bacterial translocation clearly occurs in some preclinical models of critical illness (10), human data has generally remained inconclusive or not supportive of this as a common phenomenon seen in critically ill patients, although it likely occurs in select pathophysiologic conditions (11;12). A search for how intestine-derived mediators caused distant injury led to the gut-lymph hypothesis. This theory postulates that toxic mediators from the gut travel through mesenteric lymphatics toward the lung where they cause remote injury. Several lines of investigation support the importance of the gut-derived lymph as being physiologically important. When the mesenteric lymph duct is ligated in multiple models of critical illness, lung injury and neutrophil activation are abrogated or prevented, and importantly, mortality is diminished or prevented (13;14). Additionally when mesenteric lymph from rats undergoing trauma/hemorrhagic shock is injected into non-manipulated rats, the rats receiving the injection develop lung injury similar to shock rats (15). Of note, gut-derived lymph typically does not contain intact bacteria, endotoxin or cytokines but rather contains protein or lipid factors that stimulate toll-like receptor 4, leading to activation of inflammatory neutrophils in the lung. Although not a part of the gut-lymph hypothesis, it has also been shown that gut-specific deletion of Mttp (a protein required for chylomicron assembly) improves survival in septic mice subjected to *P. aeruginosa* pneumonia (16), although aged animals with the identical genetic knockout have lower survival when subjected to the same insult (17).

Apoptosis

Cell death via apoptosis is an evolutionarily conserved process that is important for normal development and function. However, gut epithelial apoptosis appears to be detrimental following the onset of sepsis. Both preclinical mouse models of sepsis and autopsy studies of patients who died in the ICU demonstrate a marked upregulation in gut epithelial apoptosis compared to those who die without sepsis (18;19). Gut-specific overexpression of the anti-apoptotic protein Bcl-2 has been shown to decrease sepsis-induced intestinal epithelial apoptosis and importantly improve survival in murine models of both cecal ligation and puncture and *P. aeruginosa* pneumonia (20;21). Notably, this beneficial effect of Bcl-2 overexpression is abrogated in septic mice with cancer, suggesting that alterations in the host response caused by co-morbidities can impact gut apoptosis (22).

There is evidence that crosstalk exists between the intestinal epithelium and immune system in sepsis that results in changes in gut epithelial apoptosis. While the presence or absence of lymphocytes does not impact gut epithelial apoptosis under basal conditions, sepsis-induced gut epithelial apoptosis is significantly higher in $Rag^{-/-}$ mice (which lack lymphocytes) than wild type mice, suggesting that lymphocytes play an anti-apoptotic role in the gut epithelium that is unmasked in sepsis (23). Subset analysis demonstrates that CD4+ T cells are responsible for the anti-apoptotic effect of the adaptive immune system on the gut epithelium. In addition, when Bcl-2 is over expressed in myeloid cells, there is a decrease in the amount of gut epithelial apoptosis following sepsis in addition to improved survival (24).

Hyperpermeability

The intestinal epithelium consists of only a single layer of cells that is responsible for maintaining a perma-selective barrier that in a simplistic description is charged with keeping

out the bad and letting in the good. It performs these functions via cell-cell intramembrane protein interactions within the tight junction (25). There are several families of intramembrane proteins (claudins, Occludin, Tricellulin, Junctional Adhesion Molecule), as well as intracellular connector proteins (Zonula Occludins, myosin light chain) that link the tight junction to the intracellular cytoskeleton and allow for modulation of the space (26;27). Alteration of this space can lead to changes in intestinal permeability, and there is significant evidence that intestinal permeability is increased following sepsis and MODS (28;29).

There is increasing preclinical evidence that targeting tight junctions directly or indirectly might have beneficial effects in critical illness. When myosin light chain kinase is activated, it phosphorylates the myosin light chain causing contraction of the cytoskeleton, increasing the inter-cellular space and thereby increasing permeability. Inhibiting myosin light chain kinase in mice in the setting of binge alcohol ingestion and burn injury decreases bacterial translocation and intestinal cytokine production to levels seen in sham animals, associated with a prevention in injury-induced alterations in tight junction expression and localization (30;31). A broader strategy involves targeting global intestinal integrity. Epidermal growth factor is a cytoprotective peptide that exhibits trophic and healing effects on the intestinal mucosa. When mice are given systemic epidermal growth factor following the onset of either cecal ligation and puncture or *P. aeruginosa* pneumonia, they have improved or normalized permeability, apoptosis, proliferation and villus length. Importantly, this is associated with a significant improvement in survival, even if the drug is initiated 24 hours after the onset of sepsis (32;33). This improvement in survival appears to be mediated through the gut as transgenic mice with enterocyte-specific overexpression of epidermal growth factor have the same improvement in intestinal integrity and survival following sepsis as those that receive systemic epidermal growth factor (34).

Altering the microbiome

There is increasing recognition that microbes are not inherently good or bad, but rather alter their behavior based upon their environment. Bacteria that are present in someone's healthy microbiome for decades can became virulent if environmental cues suggest an advantage to them. Further, simply the presence of bacteria that can cause fatal disease does not inherently implicate them as being pathologic. For example, *P. aeruginosa* injected into the cecum of mice undergoing a sham operation and subsequently removed can be injected into the peritoneum of a control mouse without causing any disease. In contrast, if *P. aeruginosa* is injected in the cecum of mice subjected to a non-lethal partial hepatectomy and subsequently removed and injected into a control mouse peritoneum, the resulting mortality is 100% (35). The ability of bacteria to sense host stress, their own environment and surrounding bacterial density and alter their virulence in response has profound clinical implications (36;37). This is because microbial identification without attention to its virulence may not be sufficient for treating critically ill patients while the simple presence of bacteria is not inherently harmful. In addition, virulent bacteria can potentially cause MODS without systemic dissemination. Thus a potential complementary approach to improving the antibiotic pipeline and preventing antimicrobial resistance is to prevent bacteria from becoming virulent or reprogramming them to a non-virulent phenotype. A preclinical example of this is seen with administration of a non-antibiotic, high-molecular-weight

polymer which protects mice inoculated with typically virulent organisms from mortality by altering their phenotype (38). A further example of the how the host response is altered by the microbiome can be seen when studying germ free mice, which are raised in microisolator cages and lack an endogenous microflora. When germ free mice are given *P. aeruginosa* pneumonia, they have s significantly higher mortality compared to wild type mice (39); however, germ free mice subjected to hemorrhagic shock or ischemia-reperfusion injuries have an improved survival compared to mice with intact, normal gut microflora (40;41).

GUT FAILURE IN CRITICALLY ILL PATIENTS

Clinical diagnosis of gut failure

Symptoms of gut failure in the ICU are non-specific and are not currently included in severity scoring symptoms such as the Sequential Organ Failure Assessment score. A recent prospective multicenter study of 377 patients in the ICU requiring mechanical ventilation sought to determine whether six gastroenterological symptoms -- high gastric residual volumes, absent bowel sounds, vomiting/regurgitation, diarrhea, bowel distension and GI bleeding -- could predict patient outcome (42). None of the symptoms (43) alone was an independent predictor of mortality. However, when three or more symptoms were present at day one of ICU, there was a three-fold increase in the risk of mortality.

Additionally, analysis of patient stool samples has shown promise in predicting outcomes. In a study of nearly 500 stool samples from an ICU cohort with sepsis, it was determined that when fecal pH goes up or down by 1, the incidence of bacteremia more than triples and mortality more than doubles (44). Further, a decrease in obligate and facultative anaerobes has been shown to correlate with increased risk of mortality in patients with the systemic inflammatory response syndrome while a depleted or single pattern fecal stain for bacteria is associated with a greater risk of mortality in MODS compared to a diverse pattern (43).

Although not commonly used clinically, biomarkers have shown significant promise in diagnosing gut failure. The concentration of plasma citrulline is a marker of enterocyte functional metabolic mass, so decreased serum citrulline is a potential marker of intestinal damage. Further, intestinal fatty acid-binding protein is localized in enterocytes and is released following enterocyte damage, so an increase in this protein is also a potential marker of intestinal damage. The importance of both citrulline and intestinal fatty acid binding protein was recently shown in a series of over 100 medical intensive care unit patients, of which 15% had septic shock and 20% had ARDS (45). Elevated intestinal fatty acid binding protein on ICU admission was associated with catecholamine support, higher lactate, higher SOFA score, and higher INR, while decreased citrulline was associated with higher intra-abdominal pressure, higher C-reactive protein concentration and more frequent antibiotic use. Alterations in both were associated with higher 28 day mortality. Of note, two additional studies found increased serum intestinal fatty acid binding protein in patients with acute mesenteric ischemia (46;47) .

TARGETING THE MICROBIOME

Clinical strategies aimed at augmenting, decreasing or transplanting the microbiome are all used in clinical practice to varying degrees. Despite the widely varying intellectual basis for each of these as a potential therapeutic, each has shown some potential benefit, although their efficacy and potential unwanted side effects are still incompletely understood.

Probiotics, prebiotics and synbiotics

Since microbial diversity has been shown to be associated with outcomes in critical illness, the concept of augmenting "good" bacteria and restoring microbial ecology is potentially beneficial with the goal of restoring a normal, diverse flora. This can be done in a number of complementary ways: a) probiotics are exogenous live organisms, b) prebiotics are non-digestible nutrients that stimulate commensal bacterial growth, and c) synbiotics are a combination of probiotics and prebiotics. The theoretical benefit of each of these is multifactorial including local release of antimicrobial factors, maintenance of gut barrier integrity, competition for epithelial adherence, prevention of bacterial translocation, and modulation of the local immune response (48). Two recent meta-analyses of probiotics in over 1000 ICU patients demonstrate a reduction in the incidence of ventilator associate pneumonia, with one showing a decreased length of stay (49;50). No alteration in mortality was noted. It should be noted that the largest trial of probiotics to date showed increased mortality (16% vs. 6%) in 296 patients with severe pancreatitis (51). However, this trial has been heavily criticized (52), and does not appear to be representative of other studies of probiotics. Multiple questions remain prior to augmenting the microbiome gaining widespread usage as a strategy to improve outcomes in the ICU. These include what (if any) the optimal probiotic agent is, if combinations of agents are more beneficial, if synbiotics are superior to probiotics alone, what the ideal "dose" is and what the long-term safety profile is.

Selective Decontamination of the Digestive Tract (SDD)

In contrast to augmenting the microbiome, SDD seeks to preferentially minimize pathogenic enteral bacteria. The goal of this practice is to eradicate oropharyngeal and intestinal carriage of pathogenic microorganisms without adversely impacting the remaining microbiome on either the patient level or the ICU level. SDD includes three components: a) four to five days of parenteral antibiotics (Cefotaxime in previously healthy patients, combination therapy or anti-pseudomonal cephalosporin in patients with chronic disease), b) non-absorbable enteral antibiotics given via nasoenteric tube given throughout the ICU stay, and c) pastes or gels given to oropharynx (53). It should be noted that the term "selective" is a bit of a misnomer as this approach targets both normal and abnormal flora, while not covering multiple low-level pathogens.

For a practice that is rarely used worldwide (with certain exceptions), the data on SDD is both robust and impressive. In fact, it is a great paradox that the sheer volume of studies on this practice might be greater (and more supportive) than in almost any aspect of critical care, yet this has not translated to a change in clinical practice. Specifically, there have been over 60 randomized controlled trials and over 10 meta-analyses on SDD in over 15,000

patients, demonstrating a reduction of lower airway infection of 72% and bloodstream infection by 37% (54;55).

Given this significant literature, why is SDD not used more commonly used? The answer relates exclusively to concerns related to the development of antibiotic resistance. While the majority of studies examining this issue have not demonstrated the development of resistance (although a few have), these have generally been performed in ICUs that have low levels of antibiotic resistance at baseline (56). With increasing attention being paid to antibiotic stewardship and resistance worldwide, the fear that widespread antibiotic usage for preventive purposes will induce new and difficult or impossible to treat “superbugs” has limited adoption of SDD. Further, with an increased understanding of the importance of microbial health and diversity, it is currently unclear how these are impacted by the use of SDD in critically ill patients.

Fecal Transplant

There has recently been an explosion of interest in fecal microbiota transplant, where stool from a healthy donor is given to a recipient with the goal of restoring the microbiome to its homeostatic state seen in health. While multiple indications are currently being studied, the most convincing data are in recurrent *Clostridium difficile* infection where cure rates are three times higher than seen with conventional medical therapy without apparent side effects (57). To date, fecal transplant is not typically used in critically ill patients as antibiotic usage (which is common in the ICU) would immediately change the microbial components of a patient’s stool (either from donor or recipient) following transplant.

Nutrition

While a comprehensive review of nutritional support is outside the scope of this review, it is worth emphasizing the importance of nutritional support in the ICU, as one of the major roles of the healthy intestine is to absorb nutrients. Enteral nutrition is preferable to parenteral nutrition as enteral nutrition has beneficial effects on the gut associated lymphoid disease and mucosal health while not having the increased risk of infection associated with parenteral nutrition. Enteral nutrition should be initiated within 48 hours of ICU admission if possible.

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References

1. Mittal R, Coopersmith CM. Redefining the gut as the motor of critical illness. Trends Mol Med. 2014 Apr; 20(4):214–23. [PubMed: 24055446]
2. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. Shock. 2007 Oct; 28(4):384–93. [PubMed: 17577136]
3. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-organ-failure syndrome. The gastrointestinal tract: the "motor" of MOF. Arch Surg. 1986 Feb; 121(2):196–208. [PubMed: 3484944]

4. Helander HF, Fandriks L. Surface area of the digestive tract - revisited. Scand J Gastroenterol. 2014 Jun; 49(6):681–9. [PubMed: 24694282]
5. Clevers HC, Bevins CL. Paneth cells: maestros of the small intestinal crypts. Annu Rev Physiol. 2013; 75:289–311. [PubMed: 23398152]
6. Galperin C, Gershwin ME. Immunopathogenesis of gastrointestinal and hepatobiliary diseases. JAMA. 1997 Dec 10; 278(22):1946–55. [PubMed: 9396657]
7. Schulz O, Pabst O. Antigen sampling in the small intestine. Trends Immunol. 2013 Apr; 34(4):155–61. [PubMed: 23083727]
8. Defazio J, Fleming ID, Shakhsheer B, Zaborina O, Alverdy JC. The opposing forces of the intestinal microbiome and the emerging pathobiome. Surg Clin North Am. 2014 Dec; 94(6):1151–61. [PubMed: 25440116]
9. Xu Z, Knight R. Dietary effects on human gut microbiome diversity. Br J Nutr. 2015 Jan; 113(Suppl):S1–S5. [PubMed: 25498959]
10. Earley ZM, Akhtar S, Green SJ, Naqib A, Khan O, Cannon AR, Hammer AM, Morris NL, Li X, Eberhardt JM, Gamelli RL, Kennedy RH, Choudhry MA. Burn Injury Alters the Intestinal Microbiome and Increases Gut Permeability and Bacterial Translocation. PLoS ONE. 2015; 10(7):e0129996. [PubMed: 26154283]
11. Moore FA, Moore EE, Poggetti R, McAnena OJ, Peterson VM, Abernathy CM, Parsons PE. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. J Trauma. 1991 May; 31(5):629–36. [PubMed: 2030509]
12. Purohit V, Bode JC, Bode C, Brenner DA, Choudhry MA, Hamilton F, Kang YJ, Keshavarzian A, Rao R, Sartor RB, Swanson C, Turner JR. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol. 2008 Aug; 42(5):349–61. [PubMed: 18504085]
13. Badami CD, Senthil M, Caputo FJ, Rupani BJ, Doucet D, Pisarenko V, Xu DZ, Lu Q, Feinman R, Deitch EA. Mesenteric lymph duct ligation improves survival in a lethal shock model. Shock. 2008 Dec; 30(6):680–5. [PubMed: 18496238]
14. Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon. 2012 Dec; 10(6):350–6. [PubMed: 22534256]
15. Senthil M, Watkins A, Barlos D, Xu DZ, Lu Q, Abungu B, Caputo F, Feinman R, Deitch EA. Intravenous injection of trauma-hemorrhagic shock mesenteric lymph causes lung injury that is dependent upon activation of the inducible nitric oxide synthase pathway. Ann Surg. 2007 Nov; 246(5):822–30. [PubMed: 17968175]
16. Dominguez JA, Xie Y, Dunne WM, Yoseph BP, Burd EM, Coopersmith CM, Davidson NO. Intestine-specific Mttp deletion decreases mortality and prevents sepsis-induced intestinal injury in a murine model of Pseudomonas aeruginosa pneumonia. PLoS ONE. 2012; 7(11):e49159. [PubMed: 23145105]
17. Liang Z, Xie Y, Dominguez JA, Breed ER, Yoseph BP, Burd EM, Farris AB, Davidson NO, Coopersmith CM. Intestine-specific deletion of microsomal triglyceride transfer protein increases mortality in aged mice. PLoS ONE. 2014; 9(7):e101828.
18. Hiramatsu M, Hotchkiss RS, Karl IE, Buchman TG. Cecal ligation and puncture (CLP) induces apoptosis in thymus, spleen, lung, and gut by an endotoxin and TNF-independent pathway. Shock. 1997 Apr; 7(4):247–53. [PubMed: 9110409]
19. Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, Buchman TG, Karl IE. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med. 1999 Jul; 27(7):1230–51. [PubMed: 10446814]
20. Coopersmith CM, Stromberg PE, Dunne WM, Davis CG, Amiot DM, Buchman TG, Karl IE, Hotchkiss RS. Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. JAMA. 2002 Apr 3; 287(13):1716–21. [PubMed: 11926897]
21. Coopersmith CM, Chang KC, Swanson PE, Tinsley KW, Stromberg PE, Buchman TG, Karl IE, Hotchkiss RS. Overexpression of Bcl-2 in the intestinal epithelium improves survival in septic mice. Crit Care Med. 2002 Jan; 30(1):195–201. [PubMed: 11902262]

22. Fox AC, Breed ER, Liang Z, Clark AT, Zee-Cheng BR, Chang KC, Dominguez JA, Jung E, Dunne WM, Burd EM, Farris AB, Linehan DC, Coopersmith CM. Prevention of Lymphocyte Apoptosis in Septic Mice with Cancer Increases Mortality. J Immunol. 2011 Jul 6.
23. Stromberg PE, Woolsey CA, Clark AT, Clark JA, Turnbull IR, McConnell KW, Chang KC, Chung CS, Ayala A, Buchman TG, Hotchkiss RS, Coopersmith CM. CD4+ lymphocytes control gut epithelial apoptosis and mediate survival in sepsis. FASEB J. 2009 Jun; 23(6):1817–25. [PubMed: 19158156]
24. Iwata A, Stevenson VM, Minard A, Tasch M, Tupper J, Lagasse E, Weissman I, Harlan JM, Winn RK. Over-expression of Bcl-2 provides protection in septic mice by a trans effect. J Immunol. 2003 Sep 15; 171(6):3136–41. [PubMed: 12960340]
25. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, Tilg H, Watson A, Wells JM. Intestinal permeability--a new target for disease prevention and therapy. BMC Gastroenterol. 2014; 14:189. [PubMed: 25407511]
26. Cunningham KE, Turner JR. Myosin light chain kinase: pulling the strings of epithelial tight junction function. Ann N Y Acad Sci. 2012 Jul.1258:34–42. [PubMed: 22731713]
27. Odenwald MA, Turner JR. Intestinal permeability defects: is it time to treat? Clin Gastroenterol Hepatol. 2013 Sep; 11(9):1075–83. [PubMed: 23851019]
28. Fink MP. Intestinal epithelial hyperpermeability: update on the pathogenesis of gut mucosal barrier dysfunction in critical illness. Curr Opin Crit Care. 2003 Apr; 9(2):143–51. [PubMed: 12657978]
29. Fredenburgh LE, Velandia MM, Ma J, Olszak T, Cernadas M, Englert JA, Chung SW, Liu X, Begay C, Padera RF, Blumberg RS, Walsh SR, Baron RM, Perrella MA. yclooxygenase-2 deficiency leads to intestinal barrier dysfunction and increased mortality during polymicrobial sepsis. J Immunol. 2011 Nov 15; 187(10):5255–67. [PubMed: 21967897]
30. Chen C, Wang P, Su Q, Wang S, Wang F. Myosin light chain kinase mediates intestinal barrier disruption following burn injury. PLoS ONE. 2012; 7(4):e34946. [PubMed: 22529961]
31. Zahs A, Bird MD, Ramirez L, Turner JR, Choudhry MA, Kovacs EJ. Inhibition of long myosin light-chain kinase activation alleviates intestinal damage after binge ethanol exposure and burn injury. Am J Physiol Gastrointest Liver Physiol. 2012 Sep 15; 303(6):G705–G712. [PubMed: 22790598]
32. Clark JA, Clark AT, Hotchkiss RS, Buchman TG, Coopersmith CM. Epidermal growth factor treatment decreases mortality and is associated with improved gut integrity in sepsis. Shock. 2008 Jul; 30(1):36–42. [PubMed: 18004230]
33. Dominguez JA, Vithayathil PJ, Khailova L, Lawrance CP, Samocha AJ, Jung E, Leathersich AM, Dunne WM, Coopersmith CM. Epidermal growth factor improves survival and prevents intestinal injury in a murine model of pseudomonas aeruginosa pneumonia. Shock. 2011 Oct; 36(4):381–9. [PubMed: 21701422]
34. Clark JA, Gan H, Samocha AJ, Fox AC, Buchman TG, Coopersmith CM. Enterocyte-specific epidermal growth factor prevents barrier dysfunction and improves mortality in murine peritonitis. Am J Physiol Gastrointest Liver Physiol. 2009 Sep; 297(3):G471–G479. [PubMed: 19571236]
35. Babrowski T, Romanowski K, Fink D, Kim M, Gopalakrishnan V, Zaborina O, Alverdy JC. The intestinal environment of surgical injury transforms Pseudomonas aeruginosa into a discrete hypervirulent morphotype capable of causing lethal peritonitis. urgery. 2013 Jan; 153(1):36–43.
36. Zaborina O, Lepine F, Xiao G, Valuckaite V, Chen Y, Li T, Ciancio M, Zaborin A, Petroff E, Turner JR, Rahme LG, Chang E, Alverdy JC. Dynorphin Activates Quorum Sensing Quinolone Signaling in Pseudomonas aeruginosa. PLoS Pathog. 2007 Mar 16.3(3):e35. [PubMed: 17367209]
37. Wu L, Estrada O, Zaborina O, Bains M, Shen L, Kohler JE, Patel N, Musch MW, Chang EB, Fu YX, Jacobs MA, Nishimura MI, Hancock RE, Turner JR, Alverdy JC. Recognition of host immune activation by Pseudomonas aeruginosa. Science. 2005 Jul 29; 309(5735):774–7. [PubMed: 16051797]
38. Zaborin A, Defazio JR, Kade M, Kaiser BL, Belogortseva N, Camp DG, Smith RD, Adkins JN, Kim SM, Alverdy A, Goldfeld D, Firestone MA, Collier JH, Jabri B, Tirrell M, Zaborina O, Alverdy JC. Phosphate-containing polyethylene glycol polymers prevent lethal sepsis by multidrug-resistant pathogens. Antimicrob Agents Chemother. 2014; 58(2):966–77. [PubMed: 24277029]

39. Fox AC, McConnell KW, Yoseph BP, Breed E, Liang Z, Clark AT, O'Donnell D, Zee-Cheng B, Jung E, Dominguez JA, Dunne WM, Burd EM, Coopersmith CM. he endogenous bacteria alter gut epithelial apoptosis and decrease mortality following Pseudomonas aeruginosa pneumonia. Shock. 2012 Nov; 38(5):508–14. [PubMed: 23042193]
40. Ferraro FJ, Rush BF Jr, Simonian GT, Bruce CJ, Murphy TF, Hsieh JT, Klein K, Condon M. A comparison of survival at different degrees of hemorrhagic shock in germ-free and germ-bearing rats. Shock. 1995 Aug; 4(2):117–20. [PubMed: 7496896]
41. Fagundes CT, Amaral FA, Vieira AT, Soares AC, Pinho V, Nicoli JR, Vieira LQ, Teixeira MM, Souza DG. Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. J Immunol. 2012 Feb 1; 188(3):1411–20. [PubMed: 22210917]
42. Reintam BA, Poeze M, Malbrain ML, Bjorck M, Oudemans-van Straaten HM, Starkopf J. Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med. 2013 May; 39(5):899–909. [PubMed: 23370829]
43. Shimizu K, Ogura H, Hamasaki T, Goto M, Tasaki O, Asahara T, Nomoto K, Morotomi M, Matsushima A, Kuwagata Y, Sugimoto H. Altered gut flora are associated with septic complications and death in critically ill patients with systemic inflammatory response syndrome. Dig Dis Sci. 2011 Apr; 56(4):1171–7. [PubMed: 20931284]
44. Osuka A, Shimizu K, Ogura H, Tasaki O, Hamasaki T, Asahara T, Nomoto K, Morotomi M, Kuwagata Y, Shimazu T. Prognostic impact of fecal pH in critically ill patients. Crit Care. 2012; 16(4):R119. [PubMed: 22776285]
45. Piton G, Belon F, Cypriani B, Regnard J, Puyraveau M, Manzon C, Navellou JC, Capellier G. Enterocyte damage in critically ill patients is associated with shock condition and 28-day mortality. Crit Care Med. 2013 Sep; 41(9):2169–76. [PubMed: 23782971]
46. Thuijls G, van WK, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, Dejong CH, Buurman WA, Poeze M. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011 Feb; 253(2):303–8. [PubMed: 21245670]
47. Guzel M, Sozuer EM, Salt O, Ikizceli I, Akdur O, Yazici C. Value of the serum I-FABP level for diagnosing acute mesenteric ischemia. Surg Today. 2014 Nov; 44(11):2072–6. [PubMed: 24337529]
48. Theodorakopoulou M, Perros E, Giamarellos-Bourboulis EJ, Dimopoulos G. Controversies in the management of the critically ill: the role of probiotics. Int J Antimicrob Agents. 2013 Jun; 42(Suppl):S41–S44. [PubMed: 23664676]
49. Bo L, Li J, Tao T, Bai Y, Ye X, Hotchkiss RS, Kollef MH, Crooks NH, Deng X. Probiotics for preventing ventilator-associated pneumonia. Cochrane Database Syst Rev. 2014; 10:CD009066. [PubMed: 25344083]
50. Barraud D, Bollaert PE, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. Chest. 2013 Mar; 143(3):646–55. [PubMed: 23460153]
51. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van GH, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van RB, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Feb 23; 371(9613): 651–9. [PubMed: 18279948]
52. Expression of concern--Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Mar 13; 375(9718):875–6. [PubMed: 20226971]
53. Silvestri L, van Saene HK. Selective decontamination of the digestive tract: an update of the evidence. HSR Proc Intensive Care Cardiovasc Anesth. 2012; 4(1):21–9. [PubMed: 23440328]
54. Petros AJ, Silvestri L, van Saene HK, Zandstra DF, de La Cal MA, Viviani M, Peric M, Gullo A. 2B or not 2B for selective decontamination of the digestive tract in the surviving sepsis campaign guidelines. Crit Care Med. 2013 Nov; 41(11):e385–e386. [PubMed: 24162689]

55. Silvestri L, de La Cal MA, van Saene HK. Selective decontamination of the digestive tract: the mechanism of action is control of gut overgrowth. Intensive Care Med. 2012 Nov; 38(11):1738–50. [PubMed: 23001446]

56. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, Kuijper EJ, Leverstein-van Hall MA, Jansz AR, de Jongh BM, van Asselt GJ, Frenay IH, Thijsen SF, Conijn SN, Kaan JA, Arends JP, Sturm PD, Bootsma MC, Bonten MJ. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis. 2011 May; 11(5):372–80. [PubMed: 21420908]

57. Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, Rutks I, Wilt TJ. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Ann Intern Med. 2015 May 5; 162(9):630–8. [PubMed: 25938992]

Key Points

1. The gut is made up of an epithelium, an adaptive immune system and a microbiome. Each plays a crucial role in maintenance of health and in the pathophysiology of critical illness.
2. Toxic mediators from the gut travel through mesenteric lymphatics where they cause remote inflammatory injury. Preclinical trials have demonstrated that ligation of the lymph duct can prevent lung injury caused by gut-derived factors.
3. Gut integrity is compromised in critical illness with increases in apoptosis and permeability. Multiple preclinical studies have demonstrated that targeting gut epithelial integrity results in improved survival in critical illness.
4. The microbiome can alter its behavior based upon environmental cues. Preventing bacteria from becoming virulent or reprogramming them to a non-virulent phenotype has the potential to revolutionize the treatment of gut-derived sepsis.
5. Outside of enteral nutrition, no treatment targeting the gut is currently widely used in the ICU. Multiple techniques for modulating the microbiome are of potential interest as therapeutics.