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Pathophysiology of the gut and the microbiome in the host response

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Abstract

Objective—To describe and summarize the data supporting the “gut” as the motor driving critical illness and multiple organ dysfunction syndrome (MODS) presented at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development MODS Workshop (March 26–27, 2015).

Data Sources—Summary of workshop keynote presentation.

Study Selection—Not applicable.

Data Extraction—Presented by an expert in the field, the data assessing the role of gastrointestinal dysfunction driving critical illness were described with a focus on identifying knowledge gaps and research priorities.

Data Synthesis—Summary of presentation and discussion supported and supplemented by relevant literature.

Conclusions—The understanding of gut dysfunction in critical illness has evolved greatly over time, and the gut is now often considered as the “motor” of critical illness. The association of the gut with critical illness is supported by both animal models and clinical studies. Initially, the association between gut dysfunction and critical illness focused primarily on bacterial translocation into the bloodstream. However, that work has evolved to include other gut-derived products causing distant injury via other routes (e.g. lymphatics). Additionally, alterations in the gut epithelium may be associated with critical illness and influence outcomes. Gut epithelial apoptosis, intestinal hyperpermeability and perturbations in the intestinal mucus layer have all been associated with critical illness. Finally, there is growing evidence that the intestinal microbiome plays a crucial role in mediating pathology in critical illness. Further research is needed to better understand the role of each of these mechanisms and their contribution to MODS in children.

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Keywords

Multiple organ dysfunction syndrome; intestinal barrier; microbiome; pediatrics

Introduction

The gut is central to human well-being and disease. In its healthy state, the small intestinal epithelium covers an area of 30–40 square meters, and completely renews itself every 5–7 days (1). The highly dynamic gut epithelium serves as a barrier between a large population of gut immune cells and the greater than 100 trillion microorganisms living within the intestinal lumen, far more bacteria than there are cells in the entire host body (2).

Our understanding of gut dysfunction in critical illness has evolved greatly in the past 30 years, and the gut is now frequently referred to as the “motor” of critical illness (3). Critically ill patients may demonstrate a number of clinical findings suggestive of intestinal dysfunction, including abdominal distension, loss of bowel sounds, diarrhea, emesis, bleeding, and intra-abdominal hypertension. While intensive care unit (ICU) mortality is not predicted by any single gastrointestinal symptom, the number of symptoms is higher in ICU non-survivors than in survivors, and mortality increases three-fold when three or more symptoms are present on ICU admission (4). Intestinal biomarkers associated with gut dysfunction are also detectable in critically ill individuals. On ICU admission, increased plasma concentrations of intestinal fatty-acid binding protein (a gut-specific protein whose presence in plasma suggests gut injury), and decreased levels of citrulline (a marker of gut cellular mass) have both been associated with increased ICU morbidity and higher mortality at 28 days (5).

Translocation and gut-derived products causing distal injury

Initial interpretations of the gut as the “motor” of critical illness focused on the idea of bacterial translocation. It was hypothesized that critical illness caused intestinal hyperpermeability, resulting in the translocation of intact bacteria into the bloodstream, causing systemic disease. Although plausible, this theory has not proven to be entirely accurate (6).

There are other routes, however, of gut-derived products causing distant injury. Anatomically, gut-derived lymph flows from the mesenteric lymphatic duct to eventually join the pulmonary circulation (7). Numerous animal models of critical illness have revealed that mesenteric lymph duct ligation attenuates lung injury and neutrophil activation and importantly improves survival. Furthermore, lymph from mice subjected to trauma/hemorrhagic shock is capable of inducing lung injury and toxic clinical features in unmanipulated animals (8). Gut-derived lymph is only intermittently found to contain bacteria and typically does not contain endotoxin or cytokines (9). Rather, protein or lipid factors in gut lymph are thought to stimulate Toll-like receptor 4 (TLR4), leading to priming and activation of inflammatory neutrophils in the lung (10). Additionally, intestine-specific deletion of Mttp, a protein needed for chylomicron assembly, improves survival in mice after

P. aeruginosa pneumonia (11) although aged mice with the same genetic abnormality have worsened sepsis survival (12).

Alterations in the Gut Epithelium

Alterations to the gut epithelium may also impact outcomes in critical illness. Gut epithelial apoptosis is markedly increased in both murine models of sepsis and a human adult autopsy study in the ICU (13). Importantly, overexpression of the anti-apoptotic protein Bcl-2 in the intestinal epithelium in transgenic mice significantly improves survival in models of both polymicrobial abdominal sepsis and *P. aeruginosa* pneumonia (14,15). In addition, enterocyte-specific overexpression of epidermal growth factor also limits enterocyte apoptosis, restores villus length, and improves survival in sepsis (16).

Intestinal hyperpermeability is a hallmark of critical illness (17). Tight junction proteins form adhesions between neighboring cells that typically limit paracellular flux, and alterations to these structures are associated with increased gut permeability. In addition, the protein myosin light chain kinase (MLCK) regulates the contraction of the actin-myosin ring that interacts with cell adhesion molecules. When this ring contracts after MLCK-mediated phosphorylation, tight junctions are effectively pulled apart, thereby increasing paracellular permeability. Inhibition of MLCK prevents changes in adhesion molecule expression and decreases bowel inflammation in a murine burn model (18).

The intestinal epithelium is shielded from luminal contents by a protective layer of mucus. During critical illness, the mucus layer is damaged with altered hydrophobicity (19). Mucus protects against not only intraluminal organisms, but also against pancreatic digestive enzymes. Decreased mucus production, coupled with increased intestinal permeability, may facilitate some degree of pancreatic autodigestion of the gut epithelium (20). Enzymatic injury can then potentially further increase permeability, creating a positive feedback loop of worsening gut integrity.

Intestinal microbiome

Recently, there has been increasing recognition that the intestinal microbiome – the complex ecosystem of bacterial species living within the intestinal lumen – plays a crucial role not only in maintaining general health, but also in mediating pathology in critical illness. Microbial diversity and robustness appear to be critical for maintenance of health. However, the microbiome contains organisms that are pathogenic or may become pathogenic depending upon host conditions. Clinical efforts to date have focused on augmenting “good” bacteria or microbial diversity while decreasing “bad” bacteria.

Probiotics are live bacteria given in an attempt to improve human health. Conceptually, probiotics may exert a benefit by increasing the local release of antimicrobial factors, favorably modulating the immune response, and competing against pathogenic bacteria for epithelial adherence. Two recently published meta-analyses suggest that administration of probiotics lowers the incidence of ventilator associated pneumonia, without reducing overall mortality (21,22). However, optimal probiotic composition, dose and timing remain unknown.

Microbial diversity also appears to be correlated with outcomes. A recent study of adults scheduled to undergo allogeneic hematopoietic stem cell transplantation stratified patients into three groups based on the diversity of organisms found in their stool samples (high, intermediate, and low diversity). After transplant, patients were followed for three years. Survival directly correlated with the degree of microbiome biodiversity with high diversity groups showing the highest survival (23). In addition, fecal microbiota transplants have proven tremendously effective in the treatment of refractory *C. difficile* colitis, a condition highlighted by a lack of colonic biodiversity. Fecal transplantation seeks to completely repopulate the microbiome with all of the organisms present in a healthy donor. Compared to oral vancomycin, bowel lavage with a liquid suspension of stool is associated with a three-fold increase in cure rate for refractory *C. difficile* colitis, associated with minimal adverse effects and a restoration of gut microbial diversity (24). Although not directly relevant in the ICU, these findings suggest that microbial diversity may be a future target in critically ill patients.

In contrast to probiotics and efforts to improve microbial diversity, selective decontamination of the digestive tract (SDD) involves the administration of non-absorbable oral and enteral antibiotics along with short-course systemic antibiotics. SDD attempts to alter the microbiome present in the gastrointestinal tract to prevent pulmonary or bloodstream infections caused by pathogenic intestinal flora in the ICU. SDD has been extensively studied in randomized trials, and has proven effective at decreasing both infection and ICU mortality (25). Despite this, worldwide adoption of SDD has been minimal outside of select countries due to concerns regarding the development of antibiotic resistance induced by this practice.

Importantly, the microbiome appears to respond to host environmental cues. As an example, when *P. aeruginosa* is injected into the cecum of mice undergoing a sham operation and then later removed, it can be injected into the peritoneum of a control mouse without morbidity or mortality. However, if *P. aeruginosa* is injected in the cecum of mice subjected to a partial hepatectomy and then later removed and injected into a control mouse peritoneum, mortality is 100% (26). This suggests that gut bacteria are able to sense host stress and increase virulence factors in response. This has profound clinical implications because pathogen identification without attention to microbial virulence may not be sufficient for treating critically ill patients and further, virulent bacteria can potentially cause sepsis and remote organ failure without systemic dissemination. Notably, when expression of bacterial virulence factors is prevented by administration of a non-antibiotic, high-molecular-weight polymer, mice inoculated with typically virulent organisms are protected from mortality (27).

Conclusion

The relationship between intestinal dysfunction and critical illness is supported by data from both animal models and clinical studies. These data suggest that translocation of bacteria and other gut-derived products via the bloodstream and the lymphatics may precipitate critical illness and cause distant organ injury. In addition, research has linked critical illness with gut epithelial apoptosis, intestinal hyperpermeability and perturbations in the intestinal

mucus layer. Finally, there is growing evidence that alterations in the intestinal microbiome may also contribute to critical illness and organ injury. Further research is needed to better understand the role of each of these mechanisms and their contribution to multiple organ dysfunction syndrome in children (Table).

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Table

Identified Knowledge Gaps and Potential Opportunities for Study

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- The potential for gut-derived lymph to mediate pediatric multiple organ dysfunction syndrome (MODS) remains to be established. Such insight may be valuable as this may offer a target for therapeutic benefit.
 - The mechanisms triggering gut epithelial apoptosis in pediatric MODS need to be better understood. Such an understanding may foster the development of strategies to modulate intestinal cell death, and thereby, offer the potential to prevent or decrease morbidity in critical illness.
 - There is a need to more clearly elucidate the mechanisms through which gut hyperpermeability is mediated and to develop strategies to restore gut barrier function in pediatric critical illness.
 - Studies assessing the relationship between microbiome virulence and diversity and the development of pediatric MODS may provide meaningful insight to inform the development of therapeutic interventions.
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