Microbiome in Critical Illness

Nathan J. Klingen-smith
Surgical Critical Care Fellow
Department of Surgery and
Emory Critical Care Center
Emory University School of
Medicine
Atlanta, Georgia, USA

Nathan.john.klingensmith@emory.edu

Craig M. Coopersmith
Director Emory Critical Care
Center and Professor of
Surgery
Department of Surgery and
Emory Critical Care Center
Emory University School of
Medicine
Atlanta, Georgia, USA

cmcoop3@emory.edu

The Intestinal Microbiome in Critical Illness

Critical illness alters the intestinal microbiome, resulting in a loss of microbial diversity and induction of a pathobiome. Manipulating the intestinal microbiome offers a potential treatment approach in ICU patients.

The intestinal microbiome is comprised of diverse, robust microbial communities within the intestine, modified by the host's interaction with the environment (Amon and Sanderson 2017). Increasingly, research links alterations in the microbiome to maintenance of health and pathophysiology of disease. Critical illness is no exception. Given the lack of therapies aimed at the host response in critical illness combined with pathologic alterations in the microbiome seen in the ICU, treatment directly targeting the intestinal microbiome serves as a potential avenue for therapy in critically ill patients.

The Intestinal Microbiome in Health

The intestinal microbiome is composed of all microbes (bacteria, fungi, and viruses) that occupy the intestinal lumen. The number of bacteria present in the gut lumen equals the number of the cells in the human body, yet with nearly 100 times the number of genes (Li et al. 2014; Sender et al. 2016). Starting even before birth, the microbiome begins to be established (Younge et al. 2019) and is shaped by every host interaction with its environment. As the host develops, a baseline proportion and diversity of bacteria takes hold for each human, predominantly in the phylogenic families of *Bacteroidetes* and *Firmicutes*

(Dethlefsen et al. 2006). The vast majority of these bacteria act as commensal organisms aiding the host in nutrient absorption and vitamin production (Eckburg et al. 2005; Qin et al. 2010), while assisting in enterocyte maintenance and immune function and diversity (Morrison and Preston 2016; Zegarra-Ruiz et al. 2021). Bacterial products can have profound influence on human health. A group of metabolites of particular interest are short chain fatty acids (SCFA) (Pickard et al. 2017). These bacterial fermentation products are found within the lumen of the intestinal tract and are used for signalling between the microbiota and the host and can serve as an energy source for intestinal epithelial cells (Corrêa-Oliveira et al. 2016).

The determinants of microbiome health relate in large part to its ability to maintain microbial diversity and adapt to the host environment in a manner that is mutually beneficial. There is a rapid expansion of microbial diversity in early age (Dominguez-Bello et al. 2019) followed by relative stability for the majority of life (O'Toole and Jeffery 2015). Bacterial diversity within a host (α diversity) and the uniqueness of microbial populations is associated with normal gut function and health. As a person ages, loss of Bacteroides populations, high diversity and uniqueness, and maintenance of rare bacterial taxa are all associated with improved all-cause mortality (Wilmanski et al. 2021).

The Intestinal Microbiome in Critical Illness

Disruption of gut microbial diversity and

homeostasis is associated with disease. The intestinal microbiome has been shown to be associated with multiple chronic disease states. Diabetes, atherosclerosis, inflammatory bowel disease, and even cancer treatment are all influenced by the microbiome (Halfvarson et al. 2017; Sivan et al. 2015; Vrieze et al. 2012; Wang et al. 2015).

Notably, critical illness is associated with acute changes in the microbiome (McDonald D et al. 2016). The symbiotic relationship between the host and gut microbiome are altered by both the disease state itself as well as secondarily by treatments instituted in the ICU for other reasons. This results in the commensal microbiome changing in character to one that is detrimental to the host, globally termed the pathobiome (Alverdy and Krezalek 2017). The pathobiome is characterised by a lack of overall microbial diversity and loss of predominant commensal organisms to those in pathogenic phyla *Proteobacteria* (Miniet et al. 2021). The collapse of the normal microbial communities in the setting of critical illness starts nearly immediately (Krezalek et al. 2016). The robust diversity is quickly replaced by ultra-low diversity pathogens that can sense host stress and upregulate their virulence factors (Babrowski et al. 2012). Transition to this low diversity population of intestinal *Proteobacteria (Escherichia coli, Pseudomonas spp., Klebsiella spp.)* is associated with higher morbidity and mortality in ICU patients (Freedberg et al. 2018). The mechanisms of these changes are multifactorial. Critical illness, in and of itself, induces rapid

changes to the microbiome as seen in both trauma patients and in pre-clinical models. Many components of ICU management unfortunately also indirectly adversely impact the microbiome. A partial list of treatments initiated in critical illness that have been shown to alter the microbiome include antibiotics, vasopressors (which alter splanchnic blood flow), proton pump inhibitors, opiates and route of/absence of nutrition.

As bacterial populations are lost, their metabolites are also lost. Stool SCFA levels are decreased in critically ill patients (Valdés-Duque et al. 2020). The loss of SCFA-producing resident microbes can potentially have multiple effects during sepsis. Loss of SCFA may contribute to changes in sepsis-induced intestinal hyperpermeability which has been associated with increased sepsis mortality (Feng et al. 2018; Yoseph et al. 2016). Microbiota-derived SCFA also signal with the local immune system to regulate mucosal inflammation through regulatory T-cells providing a protective effect during infection (Bhaskaran et al. 2018). Additionally, in a mouse pneumonia model, antibiotic depletion of the intestinal microbiome leads to higher mortality to *Klebsiella pneumoniae* pneumonia which is reversed when animals are given oral SCFA supplementation (Wu et al. 2020).

Though critical illness induces changes in the microbiome, the baseline composition of the gut microbiome also plays a role in how a host responds to infection. The intestinal microbiome shapes the composition of the mucosal immune system through constant interface and sampling along the luminal border. This interaction facilitates immunological tolerance to commensal organisms, while also preparing the immune system for pathological invasion (Round and Mazmanian 2009). The presence of specific bacteria can directly alter immune function in response to critical illness and potentially alter ICU mortality. We recently demonstrated this in a mouse model of polymicrobial intra-abdominal sepsis,

using genetically identical animals from different vendors. Despite having the same genetic composition, mice with different microbiomes had a marked difference in survival from sepsis, with improved mortality in those with a more complex baseline microbiome. This was associated with increased effector and central memory T cells in the animals with a more diverse microbiome. When the animals were co-housed for three weeks, all animals developed a similar microbiome (as mice

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eat each other's stool), and immunological and mortality differences disappeared (Fay et al. 2019).

Part of the feedback loop for intestinal microbiome tolerance and establishment of commensal colonisation is through mucosal immunoglobulins, specifically IgA (Macpherson et al. 2018). Intestinal microbiota induce production of IgA and this immunoglobulin is able to bind to pathogens and prevent their binding to mucosal surfaces to prevent disease, as well as allowing for commensal organism proliferation. This IgA induction is specific for bacteria present in the intestinal lumen and can have protective effects in critical illness. Mice exposed to bacteria in the phylum *Proteobacteria*, produce more IgA that is specific to these pathogenic bacteria and are protected against intra-abdominal sepsis (Wilmore et al. 2018).

Manipulation of the Microbiome
Due to its putative role in mediating mortality in critical illness, the microbiome has recently been proposed as a potential target

for treatment in the ICU attempting to shift gut dysbiosis back to normal homeostasis. A number of different approaches have been investigated toward manipulating the microbiome including a) probiotics, b) prebiotics, c) fecal microbial transplant (FMT), d) enteral nutrition and e) selective decontamination of the digestive tract (SDD). Probiotics are a group of commensal bacteria that may be beneficial for the gut and systemic health in various disease states including critical illness. Multiple studies have been performed evaluating the impact of probiotics in the ICU. A meta-analysis of 30 studies with nearly 3000 patients involving probiotics and synbiotics in adult critically ill patients demonstrated a decrease in ventilator associated pneumonia seen with probiotics without changes in mortality, length of stay or diarrhoea (Manzanares et al.2016). The benefit seemed specific to probiotics as opposed to synbiotics (a combination of probiotics and prebiotics), although the data for synbiotics was limited. Unfortunately, there was significant heterogeneity in these studies, as there is not a standard protocol between studies for the type of bacteria administered, when they are given, or the dose. In addition, there may be such baseline inter-patient endogenous microbiome variability that it would be hard to know de novo which probiotic regimen may provide a benefit and if that benefit would last (Zmora et al. 2018). Furthermore, patients in the ICU, especially those with sepsis, are given antibiotics which would simultaneously eliminate infecting bacteria as well as the probiotics, limiting their ability to engraft and establish homeostatis. Together, these concerns as well as potential publication bias of studies examining probiotics and critical illness limit conclusions that can be drawn. It is also worth noting the theoretical concern of seeding the recipient patient with any bacteria delivered to the patient. A recent publication used genomic and epidemiologic evidence to demonstrate that enterally administered *Lactobacil-*

lus rhamnosus GG given as a probiotic capsule ended up causing bacteraemia in six ICU patients (Yelin et al. 2019). These concerning findings should give clinicians pause before giving critically ill patients probiotics without additional high quality data supporting their usage.

An alternative strategy involves prebiotics. Whereas probiotics contain live bacteria, prebiotics are nondigestible products intended to promote the growth of beneficial microbes in the intestine. The most common prebiotic that has been studied is dietary fibre. Fibre provides a fuel source for SCFA-producing bacteria and acts to promote improved barrier function. Animals given fibre in their diet show less mucus layer defects after having eaten a high fat, high carbohydrate diet (Schroeder et al. 2018). In septic animal models, mice given pre-treatment of a high fibre diet have improved survival compared to a low or normal fibre diet, and this is associated with a decrease in overall inflammation (Morowitz et al. 2017). Furthermore, a small pilot study of 20 ICU patients receiving broad-spectrum antibiotics randomised to receive enteral fibre or no fibre showed a trend toward increased SCFA-producing bacteria and higher SCFA levels (Freedberg et al. 2020). Together, this demonstrates a potential benefit of fibre (or other prebiotics) in critically ill patients, but this approach should be considered experimental until large well-done studies are performed with patient-centric outcomes.

An alternative approach to giving select bacterial species or promoting microbial growth is to transplant an entire intact gut microbiome. Fecal Microbiota Transplantation (FMT) is a technique in which the contents of healthy donor stool (either in liquid or capsule form) are transplanted into the intestine of a host with a diseased microbiome with the goal of restoring microbial diversity which in turn should restore host metabolism, boost host immunity, and prevent re-colonisation with pathogenic

bacteria. The most common use for FMT is in refractory *Clostridium difficile* infection (CDI). The mainstay treatment of initial CDI is still oral antibiotics. However, up to 25% of initial CDI will have a second episode despite treatment, and antibiotic therapy is often ineffective in recurrent CDI (Cornely et al. 2012). Multiple infectious disease societies recommend FMT for multiple recurrent or refractory CDI (Debast et al. 2014; McDonald LC et al. 2018) based upon studies showing complete resolution of CDI between 77% and 100% after FMT. With the success of FMT in CDI, this has led to increased interest in giving FMT in the ICU. The literature is limited only to

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case reports of ICU patients with refractory sepsis and large volume diarrhoea, but there has been some success in this setting (McClave et al. 2018). The mechanisms underlying potential FMT effectiveness in the ICU are multifactorial and include restoration of SCFA-producing bacteria that stimulate immunity to enhance pathogen clearance. In an animal model of bacterial peritonitis, mice were rescued from sepsis after FMT in an Interferon regulatory factor 3-dependent manner (Kim et al. 2020). These findings were linked to an increase in the butyrate-producing phylum *Bacteroidetes*. There are multiple barriers to using FMT in the ICU that must be overcome however before the treatment can move from its current status as experimental only. First, a large percentage of ICU patients are on antimicrobial therapy, and any antibiotic administration would alter any transplanted bacteria which narrows the population

who might benefit from FMT. Additionally, there is no uniform agreed upon standard as related to stool donor, dose or route of administration. Furthermore, there have been two case reports of multidrug resistant organisms making their way into the bloodstream of non-ICU patients receiving FMT, one of which was fatal (DeFilipp et al. 2019). Considering that most ICU patients are immunosuppressed by virtue of their critical illness and the increased risk of bacteraemia in the ICU, this emphasises the need for well-performed studies of FMT in the ICU.

Nutrition also has the potential to alter the microbiome. In healthy hosts, nutrition directly alters microbial composition and plays a significant role towards maintaining health. In the ICU, the enteral route is the preferred method of administering nutrition for multifactorial reasons including the potential for improved health within the gut microbiome and decreased bacterial translocation (Oami et al. 2019). Unfortunately, not all patients are able to utilise their gut for nutrient absorption secondary to disease states or intestinal procedures, necessitating the use of parenteral nutrition if the inability to feed the gut is expected to occur for an extended period of days. Parenteral nutrition leads to an intestinal proinflammatory state resulting in epithelial barrier dysfunction through tight junction protein downregulation and promoting *Proteobacteria* growth (Ralls et al. 2016).

While probiotics, prebiotics, FMT and nutrition have some commonality in the sense that the goal is to augment beneficial microbial flora, SDD takes the opposite approach by attempting to decrease harmful or pathogenic bacteria in the gut microbiome. SDD has been studied extensively and improves mortality in multiple randomised trials in environments with low anti-microbial resistance (Price et al. 2014). In contrast, a randomised controlled trial of over 8000 patients on mechanical ventilation in ICUs with moderate to high levels of antibiotic resistance failed to show any benefit in a

modified version of SDD (without a four day course of intravenous antibiotics), selective oropharyngeal decontamination, or chlorhexidine mouthwash (Wittekamp et al. 2018). A recent meta-analysis of 41 trials and over 11,000 patients concluded that treatment with topical prophylaxis only likely reduced respiratory infections but not mortality for those on mechanical ventilation whereas combined topical and systemic prophylaxis reduced both (Minozzi et al. 2021). Although data generally do not support SDD leading to increased antimicrobial resistance, concerns continue that intentionally altering microbial flora could potentially lead to microbial resistance, which has limited SDD use in most countries.

Conclusions

The idea of targeting the gut microbiome for therapeutic gain is no longer new. Despite the conceptual appeal of this approach, there are numerous barriers that need to be overcome to translate this into an approach which is commonly used at the bedside. These include identifying the optimal approach(es) in the correct patient population with the correct dose and route of administration of agents intended to alter the microbiome. This is further complicated by the common usage of antibiotics and other agents that directly alter the microbiome in critically ill patients, and the fact that a worsened gut barrier function in an immunosuppressed patient population leads to unique risks to microbiome manipulation in the ICU. Despite the numerous obstacles, increasing research suggests that the gut microbiome may be a promising therapeutic target in the ICU, and the future of microbiome research is promising.

Conflicts of Interest and Source of Funding

References

Alverdy JC, Krezalek MA (2017) Collapse of the Microbiome, Emergence of the Pathobiome, and the Immunopathology of Sepsis. Critical Care Medicine, 45(2):337–347.

Amon P, Sanderson I (2017) What is the microbiome? Archives of Disease in Childhood Education and Practice, 102(5):257–260.

Babrowski T, Holbrook C, Moss J et al. (2012) Pseudomonas aeruginosa virulence expression is directly activated by morphine and is capable of causing lethal gut derived sepsis in mice during chronic morphine administration. Annals of Surgery, 255(2):386–393.

Bhaskaran N, Quigley C, Paw C et al. (2018) Role of Short Chain Fatty Acids in Controlling Tregs and Immunopathology During Mucosal Infection. Frontiers in Microbiology, 9.

Cornely OA, Crook DW, Esposito R et al. (2012) Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: A double-blind, non-inferiority, randomised controlled trial. The Lancet. Infectious Diseases, 12(4):281–289.

Corrêa-Oliveira R, Fachi JL, Vieira A et al. (2016) Regulation of immune cell function by short- chain fatty acids. Clinical & Translational Immunology, 5(4):e73.

Debast SB, Bauer MP, Kuijper EJ (2014) European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for Clostridium difficile Infection. Clinical Microbiology and Infection, 20:1–26.

DeFilipp Z, Bloom PP, Soto MT et al. (2019) Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. New England Journal of Medicine.

Dethlefsen L, Eckburg PB, Bik EM, Relman DA (2006) Assembly of the human intestinal microbiota. Trends in Ecology & Evolution, 21(9):517–523.

Dominguez-Bello MG, Godoy-Vitorino F, Knight R, Blaser MJ (2019) Role of the microbiome in human development. Gut, 68(6), 1108–1114.

Eckburg PB, Bik EM, Bernstein CN et al. (2005) Diversity of the Human Intestinal Microbial Flora. Science (New York, N.Y.), 308(5728):1635–1638.

Fay KT, Klingensmith NJ, Chen CW et al. (2019) The gut microbiome alters immunophenotype and survival from sepsis. The FASEB Journal, 33(10):11258–11269.

Feng Y, Wang Y, Wang P et al. (2018) Short-Chain Fatty Acids Manifest Stimulative and Protective Effects on Intestinal Barrier Function Through the Inhibition of NLRP3 Inflammasome and Autophagy. Cellular Physiology and Biochemistry, 49(1):190–205.

Freedberg DE, Messina M, Lynch E et al. (2020) Impact of Fiber-Based Enteral Nutrition on the Gut Microbiome of ICU Patients Receiving Broad-Spectrum Antibiotics: A Randomized Pilot Trial. Critical Care Explorations, 2(6).

Freedberg DE, Zhou MJ, Cohen ME et al. (2018) Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. Intensive Care Medicine, 44(8):1203–1211.

Halfvarson J, Brislawn CJ, Lamendella R et al. (2017) Dynamics of the human gut microbiome in Inflammatory Bowel Disease. Nature Microbiology, 2, 17004.

Kim SM, DeFazio JR, Hyoju SK et al. (2020) Fecal microbiota transplant rescues mice from human pathogen mediated sepsis by restoring systemic immunity. Nature Communications, 11(1):2354.

Krezalek MA, DeFazio J, Zaborina O et al. (2016) The Shift of an Intestinal "Microbiome" to a "Pathobiome" Governs the Course and Outcome of Sepsis Following Surgical Injury. SHOCK, 45(5):475–482.

Li J, Jia H, Cai X et al. (2014) An integrated catalog of reference genes in the human gut microbiome. Nature Biotechnology, 32(8), 834–841.

Macpherson AJ, Yilmaz, B, Limenitakis JP, Ganal-Vonarburg SC (2018) IgA Function in Relation to the Intestinal Microbiota. Annual Review of Immunology, 36(1):359–381.

Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE (2016) Probiotic and synbiotic therapy in critical illness: A systematic review and meta-analysis. Critical Care, 20.

McClave SA, Patel J, Bhutiani N (2018) Should fecal microbial transplantation be used in the ICU? Current Opinion in Critical Care, 24(2):105–111.

McDonald D, Ackermann G, Khailova L et al. (2016) Extreme Dysbiosis of the Microbiome in Critical Illness. MSphere, 1(4):e00199-16.

McDonald LC, Gerding DN, Johnson S et al. (2018) Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clinical Infectious Diseases, 66(7):e1–e48.

Miniet A, Grunwell J, Coopersmith C (2021) The microbiome and the immune system in critical Illness. Ovid. Current Opinion in Critical Care, 27(2), 157–163.

Minozzi S, Pifferi S, Brazzi L et al. (2021) Topical antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving mechanical ventilation. The Cochrane Database of Systematic Reviews, 1, CD000022.

Morowitz M, Di Caro V, Pang D et al. (2017) Dietary supplementation with non-fermentable fiber alters the gut microbiota and confers protection in a murine model of sepsis. Critical Care Medicine, 45(5):e516–e523.

Morrison DJ, Preston T (2016) Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes, 7(3):189–200.

Oami T, Chihade DB, Coopersmith CM (2019) The microbiome and nutrition in critical illness. Current Opinion in Critical Care, 25(2):145–149.

O'Toole PW, Jeffery IB (2015) Gut microbiota and aging. Science, 350(6265):1214–1215.

Pickard JM, Zeng MY, Caruso R, Núñez G (2017) Gut Microbiota: Role in Pathogen Colonization, Immune Responses and Inflammatory Disease. Immunological Reviews, 279(1):70–89.

Price R, MacLennan G, Glen J (2014) Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: Systematic review and network meta-analysis. The BMJ, 348.

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