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Fecal Micobiota Transplantation to treat sepsis of unclear etiology

Sara Gaines, MD and John C Alverdy, MD

Department of Surgery, University of Chicago Medicine Chicago, IL

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Providing normal feces to the intestinal tract of a patient suffering from life-threatening infection dates back to the fourth century when the Chinese medical literature described treating food poisoning with fecal material known as “golden soup (1).” German soldiers stationed in Northern Africa during World War II reported that natives consumed camel feces to treat dysentery (2). With this historical perspective in mind, the recent and remarkable success we are witnessing with fecal microbial transplantation (FMT) to treat recalcitrant *Clostridium difficile* colitis seems to make sense. If the gut ecosystem is so disturbed that it cannot be reordered with antibiotics, FMT therapy sounds rather straightforward: reestablish the normal microbial ecosystem in the gut by introducing feces from a healthy donor. Now with data from several hundred patients suffering from *C. difficile* colitis demonstrating remarkable success, administration of an FMT, either via nasogastric tube or via colonoscopy, appears to be highly efficacious when a gut pathogen is causing life-threatening sepsis (3,4). As such, it now seems logical, if not opportune, to extent this therapeutic concept to other disorders in which a gut pathogen or community of pathogens may be causing life-threatening sepsis.

In the present study by Wurm, Spindelböck, et al. (5) three, relatively young, patients were admitted to intensive care units at Medical University of Graz in Austria for various reasons and symptomatology. During their ICU admission, each patient developed severe, high volume diarrhea. The authors proposed that the common factor linking the three patients was previous exposure to antimicrobial and steroidal therapy, both of which are known to disrupt the microbiome and cause alterations in epithelial permeability (6,7). Each patient underwent upper and lower gastrointestinal endoscopy with biopsy. Histopathologically, the biopsy specimens demonstrated near total crypt loss and severe villus blunting in the small intestine and varying severity of crypt and epithelial loss in the colon. Two of the patients underwent an extensive microbiota analysis. Fecal samples initially showed an overabundance of Proteobacteria and a diminution in Bacteriodes and Firmicutes. As the disease progressed, the diversity of the microbiota and organismal dominance underwent

Corresponding author: John C Alverdy, jalverdy@surgery.bsd.uchicago.edu.

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extreme fluctuations. The “richness” of the microbiota remained reduced compared to samples from control subjects throughout the clinical course. The predominant bacterial species varied in character with *Pseudomonas* and *Enterococcus* emerging in one patient and *Lactobacillus* and *Haemophilus* in the other prior to and after treatment with a probiotic. One patient underwent FMT consisting of 61% Bacteroides and 37% Firmicutes. The authors reported a continuous decline in stool burden and evidence of regenerating crypts and epithelial lining by day 7 following the FMT. Although *Haemophilus* colonization was initially overtaken by *Enterococcus* following the FMT, physiologic proportions of Bacteroides and Firmicutes were eventually reestablished. The authors concluded that the observed “apoptosis,” characterized by crypt and epithelial loss, may be the consequence of the physiologic alterations from a highly disturbed microbiome. In this circumstance, administration of an FMT could potentially reestablish epithelial homeostasis.

The role that the normal microbiota play to maintain epithelial structure and function is now well-established. Work from our laboratory and others has demonstrated that the microbiota plays a key role in maintaining the regenerative capacity of the intestinal epithelium (8). This appears to be especially prominent within crypts in the cecum, the area of the intestinal track with the greatest physical density and biomass of bacteria. Cecal crypts lose their microbiota in response to environmental stressors (i.e surgical injury) and antimicrobial therapy. The cecum is unique as there is closer contact between the epithelial surface and bacteria allowing for denser colonization and proximity to stem cells key regulators of epithelial structure and function (8,9). Due to this physical intimacy, it is hypothesized that the crypts may facilitate epithelial regeneration during times of stress. In our studies, tissues from cecal crypts devoid of their microbiota had abnormal stem cell activation, an increase in apoptosis, and a loss in regenerative capacity. Most importantly, loss of the normal microbiota from cecal crypts provided an opportunity for pathogenic bacteria to occupy these microhabitats and impair epithelial function. In our mouse model, as described in this clinical report, provision of an FMT restored the physiological effect of the microbiota by reoccupying the cecal crypts with their normal microbiota thereby enhancing their regenerative capacity. At least in mice, the FMT prevented colonization of crypts by pathobiota and activated the immune system to facilitate clearance of further incoming pathogenic bacteria (10). As such there is merit to consider how we might extend these finding to treat critically ill patients who suffer from gut-derived sepsis by providing them with normal microbiota in the form of an FMT. Yet we must proceed with caution, recognizing that we are indeed providing a foreign (non-self) antigenic load via the gastrointestinal track to patients known to have intestinal hyperpermeability as a recognized feature of their critically ill state.

It is becoming increasingly recognized that unavoidable therapies to care for the critically ill result in widespread destruction of the normal gut microbiome (11–13). Yet despite this, most patients recover without incident once their microbiome can refaunate as their clinical conditions improves and antibiotics are withdrawn. Yet the tipping point at which the intestinal microbiome becomes critically depleted such that intestinal pathology develops and drives the septic response remains to be determined. Point of care diagnostics to monitor the collateral damage caused by modern intensive care therapies on the intestinal track microbiota and gut barrier function are needed. The extensive analysis provided by this

report is impressive, yet costly and time consuming. As a more preventative strategy, rather than providing an FMT when patients are already displaying signs of diarrhea and sepsis, it might be wiser to provide some type of microbiome maintenance therapy as a preemptive measure. Yet first we must establish which microbiota are lost and what level of community structure and abundance is needed to maintain an “adequate” microbiome in a critically ill patient.

At first glance, the provision of an FMT to the critically ill patients described by Wurm, Spindelböck, et al. (5) appears as some form of reckless empiricism. Yet, in the context of the historical perspective, and on compassionate plea for the lives of the patients herein reported, it might have been life-saving. This report provides cautious optimism that we need to consider the gut microbiome as yet another organ that can fail in the critically ill. How we define gut microbiome organ failure and how we treat it will require further investigation. As the saying goes “No data are more convincing than those that lack a proper control group.” As such, properly controlled studies among the critically ill are needed before we embark on further empirical use of FMT to treat the yet-to-be-defined entity of “Antibiotic-associated apoptotic enterocolitis.”

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