# Influence of the Microbiome on Anastomotic Leak

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## Abstract

Despite advances in surgical technique and the expanded use of antibiotics, anastomotic leak remains a dreaded complication leading to increased hospital length of stay, morbidity, mortality, and cost. Data continues to grow addressing the importance of a functional and diverse colonic microbiome to ensure adequate healing. Individual pathogens, such as *Enterococcus faecalis* and *Pseudomonas aeruginosa*, have been implicated in the pathogenesis of anastomotic leak. Yet how these pathogens proliferate remains unclear. It is possible that decreased microbial diversity promotes a shift to a pathologic phenotype among the remaining microbiota which may lead to anastomotic breakdown. As the microbiome is highly influenced by diet, antibiotic use, the stress of surgery, and opioid use, these factors may be modifiable at various phases of the surgical process. A large amount of data remains unknown about the composition and behavior of the "normal" gut microbiome as compared with an altered community. Therefore, targeting the gut microbiome as a modifiable factor in anastomotic healing may represent a novel strategy for the prevention of anastomotic leak.

**Keywords**
- microbiome
- anastomotic leak
- healing

Despite increased attention to anastomotic leak risk factors, a tension-free anastomosis, confirmation of adequate blood supply, selective stapled versus handsewn technique, and optimization of timing of surgery after neoadjuvant chemoradiation, anastomotic leak remains a dreaded complication in colorectal surgery. The best data continue to suggest that overall incidence of anastomotic leak in colorectal surgery remains 11%, though variation in trials ranges from 1 to 24%.[1] For decades, surgeon scientists have addressed the above variables; however, the rate of clinical anastomotic leaks remains unchanged. Recently, attention to the role of gut microbiota in intestinal wound healing and its role in anastomotic leak pathogenesis has sparked new interest. While we are in the early phase of our understanding of the pathogens and mechanisms which contribute to anastomotic healing and clinical leak rates, the composition and function of the gut microbiota appear to be essential to the process of tissue healing (►**Table 1**).

Within the human body, microbes dramatically outnumber human cells. The best estimates with modern technology predict that the typical concentration of bacteria present in the large intestine approach $10^{11}$ per mL of fecal contents.[2] This innate microbiome is a complex, dynamic system easily altered by local factors and stresses. Since the 1800's, surgeons have been focused on sterilizing the gastrointestinal tract of pathogens to minimize surgical infections and complications. As far back as 1955, Isadore Cohn demonstrated this effect in dogs showing that intraluminal injection of antibiotics prevented leak in colonic anastomosis as compared with intraluminal lavage with saline.[3] Subsequently, in 1976, LeVeen et al demonstrated that oral antibiotics administered to dogs for 6 days postoperatively increased colon anastomotic tensile strength by 70% compared with control.[4] While discovery of sterile surgical technique and perioperative antibiotics initially improved patient morbidity and mortality, data now suggest that perhaps we have gone too far with this broad "slash and burn" approach and we must now consider minimizing perioperative antibiotic use to reduce bacterial resistance to modern antibiotics.[5] It is important to acknowledge that despite eradicating pathogens perioperatively, most in-hospital infections appear to arise from the patient's own intestinal microbiota, often after the suppression of beneficial bacterial populations.[6] At some level, nonselective elimination of the microbiome also may

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**Table 1** Clinical evidence for a microbial cause of anastomotic leak

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| • Clarke et al perform the first randomized prospective placebo blinded clinical trial demonstrating that oral antibiotics prevent anastomotic leak following colon surgery[13] |
| • Komen et al demonstrate that early postoperative detection by reverse transcription polymerase chain reaction (RT-PCR) for *Enterococcus faecalis* in intra-abdominal drains may be an affordable screening tool for anastomotic leak[20] |
| • Schardey et al performs a randomized prospective controlled trial of oral antibiotics in upper gastrointestinal surgery demonstrating that oral antibiotics decrease anastomotic leak rates[14] |
| • Retrospective studies mining large databases within the NSQIP (National Surgical Quality Improvement Program) demonstrate that oral antibiotics decrease rates of anastomotic leak[15] |
| • Studies from Korea demonstrate that the two most common organism isolated from sites of anastomotic leak are *E. faecalis* and *Pseudomonas aeruginosa*, the two highest collagenase producing organisms in the gastrointestinal tract[19] |
| • Wirth performs a study demonstrating that local anastomotic decontamination of the colon anastomosis with topical antibiotics (via enema) decrease anastomotic leak rates[16] |
| • Prospective randomized controlled clinical trial from Europe demonstrates that mechanical bowel prep and oral antibiotics reduces anastomotic leak rates[17] |

be considered detrimental given that the health-promoting microbiota appear to play an essential role in host immunology and defense, the details of which remain yet-to-be elucidated.

While thousands of bacterial species play a role in the innate microbial community, many of these organisms are anaerobic and belong to firmicutes and bacteroidetes phyla.[7] However, detailed studies have demonstrated that microbial composition varies substantially between individuals and can be correlated to age, gender, body mass index (BMI), and genetics.[8] Interestingly, of all of these various influences, diet appears to play the most significant role.[9] The diet one consuming allows the microbiota to process and produce metabolites that directly influence host healing and physiology.[10]

## Clinical Data Suggests that Microbes Contribute to Anastomotic Leak

Early studies have failed to implicate a single pathogen responsible for anastomotic leak. With advanced technology including culture techniques and the ability to interrogate a fecal sample by sequencing, not only can individual pathogens be identified, but their function within the entire community structure of the microbiome can now be elucidated. Together new information is emerging that suggests that beyond the identity of individual pathogens at the species level, their place within a microbial community structure, metabolism, and virulence phenotype are of greater importance to the overall pathogenesis of a given disorder, such as anastomotic leak.

This newly emerging whole community dynamic structure of the microbiome can be directly applied to surgery on the gastrointestinal tract which itself appears to have a significant effect on composition of the microbiome. Humans demonstrate a postoperative decrease in obligate anaerobes and increase populations of certain bacteria including *Enterobacteriaceae, Enterococcus, Staphylococcus,* and *Pseudomonas*.[11] Further, this alteration in composition appears almost immediate. Guyton and Alverdy reports that in vivo within just a few hours after colonic anastomosis, dominant species bacteroidetes and firmicutes drop by 90%, whereas *Enterococcus faecalis* blooms 500 folds.[12]

Clinical studies tracing back to the 1970s implicate the microbiome in wound healing. Clarke et al completed the first randomized prospective placebo blinded clinical trial which demonstrated that oral antibiotics prevent anastomotic leak following colon surgery in 1977.[13] Schardey et al subsequently remonstrated this effect in 1997 in esophagojejunal anastomoses following total gastrectomy for gastric cancer. They found in a prospective, randomized, double-blind, placebo-controlled, multicenter trial that use of topical antibiotics perioperatively decreased the anastomotic leak rate from 10.6 to 2.9%.[14] Modern data appear to also support this, and subsequent retrospective studies using the National Surgical Quality Improvement Program (NSQIP) database have demonstrated that oral antibiotics decrease rates of anastomotic leak.[15] Recently, Wirth et al demonstrated similar findings of esophagojejunal anastomosis work by Schardey et al and found that local antibiotic decontamination of colorectal anastomoses following surgical resection for rectal cancer decreased anastomotic leak rates by nearly 50%.[16] And finally, prospective multicenter data from Europe support the use of oral antibiotics with mechanical bowel preparation with a lowered risk of anastomotic leak in left-sided colon anastomoses ($p = 0.02$) as compared with mechanical bowel preparation alone.[17]

No data thus far have identified as a single pathogen for anastomotic leak, but several correlations exist. Van Praagh et al addressed this question in 2016 by mining the Dutch Trial Registry database to conduct a study of eight matched pairs of patients with and without anastomotic leak who did not differ by gender, age, neoadjuvant chemotherapy, or radiotherapy. Patients eligible underwent elective colorectal surgery with a circular stapled colorectal anastomosis, and 15 of 16 studied candidates presented for elective resection. Investigators obtained the anastomotic doughnuts from the circular stapler and cultured bacteria using 16s rDNAand MiSeq. This method provides more information compared with culture-dependent bacterial growth yielding data about

 

the structure, membership, and potential function of microbes present within a sample that may not be cultivatable. They observed an abundance of the *lachnospiraceae* family to be statistically higher ($p = 0.001$) in the group that developed anastomotic leak as compared with those who did not. They additionally found that a high BMI was associated with both a lower degree of microbial diversity and the development of anastomotic leak. The group acknowledged that while the *Lachnospiraceae* family is not a common microbe in the colon, it may be possible that in the background of a microbiome influenced by a high BMI, domination of the microbiome by *Lachnospiraceae* may reflect the ability of certain strains to proliferate when microbial diversity is deficient, thus contributing to the pathogenicity of *Lachnospiraceae*.[18]

Both *E. faecalis* and *Pseudomonas aeruginosa* have been implicated in anastomotic leak in the literature. Lee et al conducted a retrospective study to evaluate pathogens isolated from blood or peritoneal fluid in patients who developed anastomotic leak after colon cancer surgery. They found that *E. faecalis* and *P. aeruginosa* were the two most common pathogens isolated from leak sites, both of which are known to be highly collagenolytic.[19] Subsequently, Komen et al have evaluated the presence of *E. faecalis* in intra-abdominal drains following left-sided colon surgery via reverse transcription polymerase chain reaction (RT-PCR) and produce suggestive evidence that presence of this bacteria on postoperative days (PODs) 2 and 3 may represent an easy and affordable strategy to detect anastomotic leak.[20]

Data such as these suggest a linkage between diet and BMI, along with their contributions to bacterial composition and function (i.e., phenotype), as important to the pathogenesis of anastomotic leak. Multiple trials have looked at risk factors for anastomotic leak and identified both obesity, and high-fat diet as a strong risk factor for anastomotic leak. However, these studies are able to merely hypothesize the precise factors that drive this observation. Frasson et al lead the largest prospective trial on risk factors of anastomotic leak to date by examining 3,193 patients undergoing elective colon and rectal surgery across multiple hospitals. In a multivariate analysis, they identified factors such as obesity, preoperative serum total proteins, male sex, ongoing anticoagulant treatment, intraoperative complication, and number of hospital beds to be significant independent risk factors for anastomotic leak.[21] While the mechanism and direct relationship between obesity and gut microbiota composition relative to postoperative complications remain to be elucidated, compelling data suggest that obesity is a driver for the changes in composition and function of the microbiota that colonize our gastrointestinal tract.[22] In the context of anastomotic leak pathogenesis, it is highly plausible that a strong association between diet, obesity, and anastomotic leak is tied to the microbiome. It is important to note that recent studies identifying patient risks associated with anastomotic leak have largely overlooked other factors known to shift the microbiome including antibiotic exposure, recent diet changes, smoking, and weight changes. A key to uncovering causal mechanisms of anastomotic leak will be to leverage next generation technology to interrogate the microbiome at the level of its community structure, membership, and function, as well as investigating specific bacteria phenotypes, that can directly impair anastomotic healing.

## Perioperative Care Directly Shifts the Microbiome: Implication in the Anastomotic Leak

Experimental and clinical data strongly support the concept that there is a local alteration in the gut microbiota that occurs perioperatively, specifically at the site of surgical anastomosis.[23] The standard perioperative care of fasting, bowel preparation, and prolonged antibiotic use likely impacts the composition and function of the gut microbiome, in ways that are both beneficial and detrimental, though the understanding of the precise details of this response remains in its infancy (►**Table 2**).

Diet appears to be a significant factor in alteration of gut microbiota composition and function. Multiple studies have shown that long-term dietary patterns influence the dominant organisms and their phenotype within the gastrointestinal tract. These dominant organisms appear to be tied to the proportion of fiber and herbivore intake.[24,25] Further, more recent data suggest that short-term diet alterations can quickly impact the composition and function of the gut microbiome. David et al compared short-term shifts in the human gut microbiome in two dietary groups: an animal-based diet

**Table 2** Experimental evidence for a microbial cause of anastomotic leak

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| • Isadore Cohn (Cohn and Rives) performs study in dogs in which direct application of antibiotics (via intraluminal catheter) to a devascularized (ischemic) colon anastomosis prevents leak[3] |
| • Levine demonstrates that oral antibiotics administered to dogs for 6 days postoperatively increase colon anastomotic tensile strength by 70%[4] |
| • Schardey et al demonstrates that contamination of an esophagogastric anastomosis in rats with *Pseudomonas aeruginosa* causes leak and is reversed with antibiotics[14] |
| • Olivas demonstrates that *P. aeruginosa* causes anastomotic leak in the post radiated colon in rats via production of collagenase[34] |
| • Shogan demonstrates that *Enterococcus faecalis* causes anastomotic leak rats via collagenase production and activation of anastomotic tissue MMP9[35] |

 

composing meats, eggs, and cheeses and nearly no fiber versus a "plant-based diet" rich in grains, legumes, fruits, and vegetables. Patients consumed the diet for 5 consecutive days and demonstrated a dramatic change in microbial diversity within 1 day of starting the diet, which reverted within 2 days of stopping the diet. An animal-based diet, similar to the western hemisphere, "high fat and low fiber" diet, demonstrated a shift in 22 clusters of microbes whereas plant-based diet demonstrated a shift of only 3 clusters. Further, consumption of an animal-based versus plant-based diet modified the gene expressions of the bacteria present within the gastrointestinal tract, or microbial "phenotype" within the same time period.[26] Knowing that these diet-dependent changes rapidly occur makes a compelling case to examine the practice of preoperative fasting and early postoperative sugar-based clear liquid diets given their profound effect on microbial behavior.[25]

The practice of implementing a mechanical bowel preparation (MBP), defined as purgative cleansing and oral antibiotics use, prior to colon surgery remains highly debated yet exceedingly relevant for its implications in anastomotic wound healing. Undoubtedly, it alters the microbiome preoperatively in patients in many ways that are clearly beneficial but also potentially detrimental. Shifts in microbes with MBP and its efficacy to reduce postoperative infections (i.e., ileus, surgical site infections [SSIs], and anastomotic leak) are likely closely tied to the individual patient BMI and metabolism. A randomized controlled trial of patients undergoing elective colorectal surgery examined fecal bacterial composition following MBP. This study demonstrated a significant reduction in total number of bacteria including *Clostridium, Bifidobacterium, Lactobacillus,* and *Enterobacteriaceae*, but no decrease in *Enterococcus* and *Staphylococcus*.[26] Gaines et al have demonstrated that MBP leads to suppression of collagenase producing bacteria in nonobese patients but not in obese patients which may explain the higher risk of both leak rates and cancer recurrence among obese patients, particularly those consuming a high-fat western-type diet.[27]

Although it is assumed, and in many ways proven, that the use of perioperative antibiotics will cause alteration of the colon microbiome prior to colon surgery. While initially thought to be transient, these microbiome alterations may persist for up to 2 years after antibiotic exposure, characterized by decreased species diversity and increased antibiotic resistant bacterial strains.[28] This is compounded by the observation that surgery itself is known to cause shifts in the microbiome, the mechanism of which remains poorly understood. It is well know that the physiologic stress of surgery can itself cause tissue damage and ischemia remote from the anatomic site of surgery which can alter intestinal mucus production, blood flow, cytokine production, and tight junction permeability. Implications of these effects include mucus detachment from the colonic wall permissively allowing bacteria to have direct contact with intestinal epithelium. Reperfusion injury can also allow goblet cells to release mucus that was able to clear previously bound bacteria.[29] Surgery often involves the use of vasoactive medications that affect intestinal perfusion and can further alter composition of the intestinal microbiome. Mucus is a known necessity for wound healing in the gastrointestinal tract. Microbial populations present in the mucosal layer define the function of both the epithelial and immune cells present within the gut, both known factors to contribute to wound healing.[30] Multiple studies have demonstrated that exposure of the epithelium devoid of its protective mucus layer, as well as its normal protective microbiome, can result in several untoward consequences as pathogens are allowed to adhere and transmigrate. Li et al described that the mucosal layer of the gut itself contains a distinct microbial make-up with distinct communities that show different proliferation profiles and resource utilization as compared with the same microbial species in the gut lumen. Thus, the nonselective approach to eliminate the entire microbiome with both oral and intravenous antibiotics, while beneficial in many circumstances, may have unintended consequences in those patients most at risk for postoperative complications.

Another routinely unrecognized practice that may adversely affect anastomotic healing via its effect on the microbiome is the use of medications such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Shakhsheer et al described this phenomenon in a rat model where systemic morphine administration resulted in impaired anastomotic wound healing and anastomotic leaks, in association with the presence of collagenase producing *E. faecalis* on anastomotic tissues.[31] NSAIDs have also recently been implicated in wound and anastomotic healing, while this mechanism remains largely unknown and debated; in vitro and in vivo data support that NSAIDs likely impact function of the microbes and microbial dysregulation may be a correlate of anastomotic failure with its postoperative use.[32]

## A Molecular Paradigm of Anastomotic Leak Pathogenesis Driven by the Intestinal Microbiota

Our best understanding of how mechanistically the microbiome contributes to anastomotic leak has been drawn from elegant bench research which can be translated to the operating room. Schardey et al utilized a rat model of esophagogastric anastomoses and demonstrated that not only can *P. aeruginosa* lead to anastomotic leak but can be reversed with local treatment of the anastomosis with antibiotics.[33] Olivas et al further define the role of pathogens, such as *P. aeruginosa*, which can be activated by host factors present at anastomotic tissues to express collagenase, a key bacterial exoproduct that can degrade both type-I and type-IV collagens, two forms of collage that are critical for anastomotic healing. This work demonstrated that strains of *P. aeruginosa* can shift their phenotype to not only change their antibiotic resistance profile when present at sites of anastomotic tissues but can be induced in vivo to express tissue-degrading collagenases leading to anastomotic breakdown and clinical leak.[34]

Shogan et al demonstrated that anastomotic tissues of human subject undergoing colon surgery can become colonized by both *P. aeruginosa* and *E. faecalis* both of which can

 

produce collagenase when cued by local factors present at anastomotic tissues. Using an animal model, it was demonstrated that *E. faecalis* can produce collagenase that can directly degrade anastomotic type-I collagen. It also proceeds to activate tissue matrix metalloprotease-9 from its inactive proform which can then degrade type-IV collagen. *E. faecalis* which is known to produce gelatinase (GelE), contributes to the development of leak by breaking down collagen. Genetic deletion of this gene in *E faecalis* renders the pathogen unable to cause anastomotic leak in this model. Importantly, the ability to suppress collagenase in *E. faecalis* was demonstrated with the use of topically administered antibiotics though not suppressed with systemic intravenously administered antibiotic coverage.[35]

Further characterization of the model included defining the dynamic shifts in the microbiome when rats undergo anastomotic surgery alone. It is important to keep in mind that the colon environment is highly anaerobic allowing obligate anaerobes to thrive and proliferate. Simply exposing the bowel to atmospheric oxygen, in addition to the local cues present when injured, anastomotic tissues begin to undergo the process of healing. 16S rRNA sequencing was utilized to characterize microbial changes within both the lumen and tissues at the anastomosis following surgery. Over the first week, there was a 200-fold decrease and 500-fold increase in the relative abundance of *Escherichia/Shigella* and *Enterococcus,* respectively. Further, there was a predominance in expression of bacterial virulence-associated pathways of anastomotic tissues. Importantly, this alteration and virulence factor expression was not detected in the luminal contents, but only in anastomotic tissue samples, strongly suggesting that that the microbiome within anastomotic tissues are likely to play more of a role in healing, rather than species detected in the luminal contents alone.[36] *P. aeruginosa* has also been implicated in wound healing, as it, like *E. faecalis*, uses its virulence activation system to express tissue destroying enzymes via a mechanism called quorum sensing. Like many other opportunistic pathogens, it has the ability to sense changes in its environment and respond accordingly as a mechanism for nutrient acquisition, predation, and survival. Thus, bacteria that colonize an anastomosis can detect subtle changes present in this site such as cytokines, chemokines, and end products of ischemia to which they often respond with enhanced virulence (i.e., expression of the collagenolytic phenotype.[37] Like *E. faecalis*, in vivo experiments with mice have shown morphine induces a more virulent phenotype of *P. aeruginosa* which demonstrated greater biofilm production, increased antibiotic resistance, and a mucus-suppressing phenotype.[38]

As mentioned above, Olivas et al also identified that a collagenase producing variant of *P. aeruginosa* led to increased anastomotic leak in a mouse model. To mirror clinical settings, the group exposed rats to preoperative radiation, and then performed distal colon resection followed by *P. aeruginosa* rectal enema. The study found that rats exposed to preoperative radiation developed a significantly higher incidence of anastomotic leak ($> 60\%$; $p < 0.01$) when colonized with *P. aeruginosa* as compared with radiated tissues alone. Further, when comparing strains of *P. aeruginosa* recovered from leaking anastomotic tissue, the bacteria demonstrated a phenotypic shift to a more virulent organism producing collagenase.[34]

## How to Best Study and Prevent Anastomotic Leak as It Relates to the Microbiome

Advancements in the analysis of bacterial species, at the community level, strain level, and in function, have led to a rapid increase in the understanding of microbial diversity in the gut and the community structure in which they survive and proliferate. While there is little sense of what a "normal" adult gut microbiome looks like, data are accumulating to suggest that previous antibiotic exposure, BMI, previous surgery, and mechanical bowel preparation can significantly alter gut microbiota. Given the baseline characteristics of the host, combined with the magnitude and duration of the surgical injury, and the patient's microbiome in a given circumstance, manipulation by modern medicine can be an asset at 1 minute and a liability the next. Knowing this, we are forced to acknowledge the baseline lack of insight into what microbes are truly pathologic versus simply pathologic under the right conditions. It is imperative to utilize next generation technology, sequencing and bioinformatics to more appropriately design and support studies addressing bacteria community composition and behavior before, during, and after surgery. Only with this information, can we more precisely know "what we are doing right" and "what we are doing wrong" in the context of preventing postoperative infections such as prolonged ileus, SSIs, and anastomotic leak. It is important to recognize that our current approach to infection-related complications is based on crude and incomplete bacterial culture. Understanding that microbes vary significantly when studied at the regional (stomach, small bowel, and colon) and spatial (lumen, mucus, and epithelium) level, the precise environmental context from which a given sample is analyzed must be considered in all studies.[39] The most significant data to inform the process of tissue and wound healing has likely been overlooked by not considering these factors. Attention to this in future studies will help better understand how to manipulate the microbiome to the advantage of the surgical patient. This approach is likely to involve approaches that collaborate with the microbiome over the course of surgery rather than those approaches that seek to eliminate it.

Most methods today do support altering the microbiome in both composition and function to enhance healing and improve the disease processes. Microbial diversity and community interaction appear to be beneficial to gut function and healing. It is becoming increasingly clear that a more comprehensive understanding at the molecular level of the pathogenesis of anastomotic leak is needed that includes both microbial and host elements that interact during the process of healing. As emphasized above, it is likely that therapeutic intervention will center on development and maintenance of a diverse microbial community rather than elimination of certain microbes. Further, it is likely that

interventions to limit microbiota-driven collagen degradation, free radical generation, and matrix metalloprotease activation are more likely to be successful then elimination of microbes alone.

Despite the lack of understanding of the precise mechanism of anastomotic leak, novel therapies targeting microbial activated pathways have emerged and may be of clinical significance. Wiegerinck et al reported the use of a novel synthesized phosphate carrier being to prevent colonic anastomotic leak in a mouse experimental model. This compound is known to suppress bacterial collagenase production without affecting bacterial growth, thus preserving whatever beneficial role the remaining microbiota might have in the process of anastomotic healing. The rationale for this compound is based on work demonstrating that phosphate is a major growth factor for many bacteria. When intestinal lumen phosphate stores are depleted, as occurs following surgery, bacteria migrate to intracellular stores with host tissues where phosphate is rich. This invasion into host tissues requires them to express virulence, the collateral damage of which can be anastomotic tissue disruption. In this study, mice underwent a distal colonic resection and anastomosis followed by rectal enema of *E. faecalis*, to expose anastomotic tissues to a known "leak pathogen." Mice were randomly assigned to receive a phosphorylated carrier, ABA-PEG20-Pi20 or its unphosphorylated counter ABA-PEG20k in their drinking water, and mice were followed for development of anastomotic leak. In vitro studies with the two carriers indicated that the phosphorylated carrier lead to a near complete inhibition of collagenase production, without suppressing bacterial growth in *E. faecalis*. Mice drinking the phosphorylated carrier demonstrated a twofold increase in local phosphate concentration at anastomotic tissues and leak rates decreased from 8 of 15 to 3 of 15 mice ($p < 0.001$).[40]

Clinically, it is important to acknowledge that the Enhanced Recovery Pathway (enhanced recovery after surgery [ERAS]), as demonstrated over the last several years, can decrease overall cost and hospital length of stay features many pillars that effect the colonic microbiome. Attention to early cessation of smoking, shortened NPO times, perioperative carbohydrate (and possibly phosphate containing) loading, and opioid sparing are all factors which are known alter the microbiome. Taking all of this into consideration, it is possible that one reason ERAS has led to success in reducing overall complication may be via its effects on the gut microbiota.[41]

Collectively, the work above strongly suggests that the microbiome is a modifiable variable that may be exploited to improve the outcome of our patients. No doubt, surgical technique, including blood flow and tension, contributes to anastomotic healing; however, the extent to which local cues present at anastomotic construction sites induce bacteria to adhere, invade, and cause impaired healing needs to be investigated. Further work is needed to determine exactly how alterations in this system contribute to anastomotic failure; however, designing preventative approaches to limit the incidence of infection-related complications following anastomotic surgery will be informed by a more comprehensive understanding of the microbiome in the process of healing. The promise of this approach lies in the technologic advances now available in genetic sequencing, metabolomics and bioinformatics.

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