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Current Opinion in Clinical Nutrition and Metabolic Care: Nutrition and the Gastrointestinal Tract

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Abstract

Purpose of review—The purpose of this review is to highlight new research findings in the complex bidirectional crosstalk that occurs between the intestinal microbiome and the host immune system in the context of surgical recovery and outcomes.

Recent findings—Significant evidence has been generated emphasizing the central role of the intestinal microbiome on surgical outcomes such as wound healing, surgical site infections and anastomotic leak. Current preventive strategies including the use of some parenteral antibiotics, may actually exacerbate the problem by selecting for drug-resistant pathogens.

Summary—A delicate balance exists between the human host and its microbial counterparts that is directly related to post-surgical healing. This balance can be easily altered in favor of the pathogen through peri-operative and surgical interventions leading to intestinal dysbiosis and loss of colonization resistance. Current strategies to prevent infectious complications with the escalating use of broader and more powerful antibiotics is not an evolutionarily stable strategy. A more complete understanding of the ecological and molecular interactions of the host with its microbiome is necessary to uncover new therapeutic strategies that preserve the composition and function of the intestinal microbiome and constrain virulent pathogens through the course of surgical injury.

Keywords

intestinal microbiome; wound healing; wound infection; anastomotic leak

Introduction

Everything affects the microbiome and microbiome affects everything, from early human development to health, minor illness, chronic disease and their respective outcomes. The recent discoveries of the countless networks of interactions of the intestinal microbiome with the various physiologic systems are beginning to shed light on the scope of the dependence of our health on our microbial partners.(1–3) The intestinal microbiome has been shown to exert a profound influence on the immune and neuroendocrine systems, which in turn alter

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the microbiome in an endless iterative loop of ongoing signal exchange. However, these interactions remain descriptive and whether the intestinal dysbioses associated with disease states are the cause or consequence of the shifts in the intestinal microbiome is unknown.

Interaction networks between the intestinal microbiome and the human host are especially important to consider in the realm of recovery from surgery. While the outcomes of surgery and surgical recovery are largely dependent on operative technique and adherence to strict best practice guidelines, we are beginning to appreciate the impact of the intestinal microbiota on surgical recovery and complications. Health-promoting intestinal microbes are essential modulators of the immune, metabolic and neuroendocrine responses to stress of injury and hence to surgical recovery.(2,4,5) A precise degree of self-limiting inflammation is crucial to tissue repair and regeneration, while exaggerated inflammatory activation can lead to chronic inflammatory conditions, fibrosis and cancer.(6) Disruption of the intestinal microbiome with surgery and common peri-operative treatments, such as intravenous antibiotics, lack of enteral nutrition and use of opioid pain medications, have been shown to lead to abnormal inflammatory response, weakening of the epithelial barrier, translocation of bacteria (and their secretome), and further exacerbation of local and global inflammation; at the same time, disruption of the neuroendocrine signaling imposed by surgical stress (and potentially changing microbiome composition and function) can lead to a wide variety of derangements, from gut-sensory motor dysfunction to alterations in behavior and mental health.(2)

In this review, we will address recent advancements in knowledge pertaining to the influence of surgical and peri-operative stress on the intestinal microbiome, as well as the effects the changing microbiome imparts on the outcomes of surgical recovery.

Stress of surgery and peri-operative interventions alter the composition and function of the intestinal microbiome

Tissue injury associated with surgical intervention has an independent effect on the intestinal microbiome composition. Tissue injury, ischemia, decreased oxygen carrying capacity due to blood loss, all have been previously shown to have a profound and variably durable effect on the make-up of the intestinal microbiome. Previous work from our lab has demonstrated that distal colon resection and anastomosis in rats without the use of antibiotic prophylaxis result in significant changes in the tissue associated microbiota that does not correlate with the bacterial composition of the luminal contents.(7) In this study, we found a 500-fold increase in the abundance of *Enterococcus faecalis* present at the anastomotic site. This bacteria, which can adopt either a commensal or pathogenic lifestyle, is commonly associated with surgical infectious complications, such as anastomotic leakage and wound infection. In addition to technical aspects of surgery, patient related factors such as smoking, obesity and insulin resistance have been independently shown to impact the composition of the intestinal microbiome, and thus their effect on healing may be via how they shape and affect the microbiome.

While the stress of surgery alone changes the intestinal microbiome, the consequences of peri-operative therapies, such as antibiotics, lack of enteral nutrition, opioids and gastric acid

reducing medications, have proven to have an even more pronounced effect on the microbiome. For one, antibiotic administration as prophylaxis before and after surgery has the potential to collapse the health-promoting intestinal microbiome, thereby impairing the ability of the intestine to provide the ecologically important colonization resistance, the consequences of which can allow virulent and often resistant pathogens to bloom. A post antibiotic effect phenomenon has been describe in which this effect persists long after antibiotic administration is stopped.(8,9) Lack of enteral nutrition characteristic of peri-operative time frame has been shown to not only alter the intestinal microbiome composition, but also to weaken the epithelial barrier function.(10) For example, in a model of significant intestinal resection with anastomosis in piglets, peri-operative antibiotic administration combined with lack of enteral nutrition resulted in the most dramatic shift in diversity and relative abundance of intestinal microbes when compared to intestinal resection alone.(11) While antibiotic administration is clearly associated with rise of resistance among the intestinal bacteria, recent findings additionally associate gastric acid reducing medications, such as proton pump inhibitors and H2 blockers, with increased risk of intestinal carriage of resistant pathogens, namely extended spectrum beta lactamase (ESBL) producing *Enterobacteriaceae*.(12) Lastly, opioids such as morphine and its derivatives, which are used almost ubiquitously to control post-operative pain, have a profound impact on the composition and function of the intestinal microbiome.(13) In addition, systemic morphine exposure compromises the intestinal barrier function leading to bacterial translocation and a pro-inflammatory phenotype, which can be transferred through the route of fecal microbiota transplant (FMT) to mice naïve to morphine. Banerjee et al further corroborate that morphine effect is mediated by the intestinal microbiota through the restoration of gut immune homeostasis with FMT from healthy placebo-treated mice transferred into those treated with morphine.(13) Our lab has previously demonstrated that systemic morphine administration has a potential to transform pathogenic bacteria into a more virulent phenotype.(14–16) In this work, intestinal *Pseudomonas aeruginosa* inoculation following laparotomy (with or without partial hepatectomy) in mice implanted with subcutaneous morphine pellet led to enhanced virulence and shift to a lethal phenotype.

The imbalance in the mutualistic relationship between the host and its microbial counterparts due to the above peri-operative treatments, coupled with the stress of surgery, gives rise to an altered intestinal milieu, impaired barrier and immune function.(17) These alterations have profound implications on surgical outcomes such as wound healing, surgical site infections and anastomotic leak.

Intestinal microbiome and surgical site infections

Although the impact of the intestinal microbiome on wound healing is largely unknown, novel findings support the importance of our microbial counterparts in this process. Poutahidis et al compared wound healing speed in mice undergoing a cutaneous biopsy procedure after being fed a standard chow or chow supplemented with a probiotic, *Lactobacillus reuteri*, known to modulate immune response.(18) Animals supplemented with the probiotic displayed more than twice the speed of wound healing, when compared to the controls. Interestingly, the authors found that this phenomenon was associated with upregulation of neuropeptide oxytocin, while wound healing was delayed in oxytocin

deficient mice, strengthening the role of oxytocin as a global regulatory hormone and further providing evidence for the importance of the gut-brain axis to post-surgical outcomes. Furthermore, intestinal microbiome has been recently linked to modulation of neutrophil ageing process, which controls their pro-inflammatory properties.(19) Depletion of health promoting microbiota has been shown to promote generation of overactive older neutrophil subsets, leading to exaggerated tissue injury.

In addition to global immune modulation, intestinal microbiota play an underappreciated role in the feared complication of surgical site infection. A randomized controlled trial performed in the 1970s by Clarke et al assigned patients who underwent elective colorectal operations to either oral antibiotics (erythromycin and neomycin) or placebo after mechanical bowel prep. The researchers found a significant decrease in surgical site infection rate from 35% in the placebo group to 9% in the oral antibiotic group.(20) These early findings emphasize the role of the intestinal microbiota in post-operative wound infections. Although intraoperative spillage of the intestinal contents and intra-operative contamination from the environment clearly predispose to surgical site infections, intraoperative wound cultures have been shown not to be useful predictors of post-operative wound infections.(21,22) Wound infections that occur in the absence of intestinal content spillage, intestinal manipulation or intra-operative contamination are common. As an example, *Methicillin resistant Staphylococcus aureus* (MRSA) wound infections continue to occur even with strict adherence to pre-operative screening, intranasal decolonization and targeted parenteral antibiotic prophylaxis.(23,24) These infections often occur late and are especially disastrous when associated with the presence of a foreign body, such as a hip prosthesis or aortic graft. The mechanism by which these microbes gain access to the surgical site remains elusive. Thwaites and Gant proposed a fascinating “Trojan horse hypothesis” pertaining to such infectious complications caused by MRSA.(25) They believe that this microbe might have the ability to survive and travel within a leukocyte to distant sites of injury/inflammation and cause metastatic infections. This hypothesis has yet to be confirmed, however it raises important questions regarding the ability of potential pathogens colonizing the intestine to cause distant surgical site infections in the absence of direct contamination.

Stabilization of the intestinal microbiome using probiotics and synbiotics in order to prevent post-operative infectious complications has garnered a lot of recent interest.(26) However, clinical studies show mixed results largely due to the heterogeneity of the administration schedules and the types of probiotics and synbiotics used. A recently performed systematic review with meta-analysis of 28 randomized controlled trials involving 2511 patients revealed that the use of these substances has the potential to reduce the incidence of wound infections.(27) Specifically, studies using combination of two or more probiotic strains were associated with significant outcomes. This is of no surprise, as one bacterial strain is unlikely to promote reinstatement of the complex community structure and function of the health-promoting intestinal microbiome. Nevertheless, these findings provide further support to the importance of the intestinal microbial homeostasis on post-surgical wound healing and complications.

The Microbiome and anastomotic leak

Anastomotic leak is a dreaded complication of intestinal resection which is commonly ascribed to poor surgical technique resulting in tissue ischemia and dehiscence. However compelling evidence points to the intestinal microbiobes as the instigators of anastomotic complications. Although findings linking microbes to anastomotic leakage have existed for over 70 years, this concept is gaining a recently renewed interest due to widespread attention to microbiome research. One of the original works on the topic was performed by Cohn and Rives who demonstrated that devascularized colonic anastomosis in dogs resulted in attenuated mortality rate when combined with the use of pre-operative oral antibiotics and mechanical bowel preparation, implicating the microbes as the causative agent of anastomotic leak.(28,29) These findings were later corroborated by others. However, pre-operative oral antibiotic prophylaxis has been largely abandoned over the years in favor of intravenous antibiotic prophylaxis, despite of strong empiric evidence suggesting benefit of oral antibiotics. Mechanical bowel preparation continues to remain in use, although evidence suggests that it may lead to disruption of the intestinal microbial community and colonization resistance against pathogens, without actual decrease in microbial abundance. (30) Further complicating the issue, parenteral antibiotics and mechanical bowel preparation ubiquitously used as prophylaxis before intestinal surgery have an untoward effect of selecting for drug-resistant organisms.

The recently renewed interest in intestinal microbiome has led to new evidence confirming the important role of bacteria in pathogenesis of anastomotic leakage.(31) Reintroduction of oral antibiotics to the pre-operative prophylactic regimen in some centers has again shown to not only result in reduced rates of anastomotic complications, but also surgical site infections, post-operative ileus and sepsis.(32,33) Our laboratory's work recently provided further evidence of a direct link between anastomosis-associated microbes and anastomotic leak. Analysis of anastomotic tissues complicated by leaks demonstrated a nearly 500-fold increase in abundance of commensal *Enterococcus* species.(7) In a rat model of colon resection, *Enterococcus faecalis* colonizing the distal colonic anastomosis was found to display an increased collagen-degrading phenotype contributing to tissue degradation and anastomotic leak. In this same model, application of topical antibiotics prevented anastomotic leaks.(7,34) Furthermore, bacteria present on anastomotic tissues in human samples were found to display a collagen-degrading phenotype even after mechanical bowel preparation and parenteral antibiotic prophylaxis as per recommended best practice guidelines. Other studies have shown that the detection of *Enterococcus faecalis* in drain fluids after anastomotic colorectal surgery correlated with anastomotic leakage.(35) Along the same line of reasoning, exposure of colonic anastomotic tissues to pathogenic bacteria, such as *Pseudomonas aeruginosa*, leads to activation of a virulent phenotype characterized by the ability of *P. aeruginosa* to express increased collagen-degrading activity and cause anastomotic leak.(36)

Evidence from both animal and human research strongly suggests a critical role of the intestinal microbiota on anastomotic healing and outcomes. Commensal microbes and pathogenic bacteria colonizing the intestine have the potential to acquire an aggressive and virulent tissue degrading phenotype when subjected to the stress of intestinal resection,

anastomosis and peri-operative treatments, such as prophylactic parenteral antibiotics and opioids, resulting in anastomotic breakdown.

Conclusion

In this review, we outline the importance of maintaining the delicate balance between the human host and its microbial counterparts for the purposes of healing and recovery from surgery. This balance is easily tipped in favor of the pathogen through medical and surgical interventions with important consequences to post-surgical healing and infectious outcomes. Evidence suggests that a fraction of infectious complications of surgery, that have been solely ascribed to surgical technique errors in the past, may in fact be related to intestinal dysbiosis. Although it is not currently possible to eliminate the use of peri-operative antibiotics or the use of opioids for post-operative pain control as they have their obvious benefits, it is time to rethink the current strategies of prevention of post-surgical infectious complications. Indiscriminate elimination of the gut microbiota is not an evolutionarily stable strategy.(37) The risks of loss of colonization resistance and selection of virulent and resistant pathogens is a major unwanted consequence. To date, the use of selective digestive decontamination, probiotics, prebiotics, and synbiotics have been largely unsuccessful due to lack of detailed understanding of the precise effect these interventions have on the community structure and function of the intestinal microbiota. Fecal microbiota transplant has shown great results in certain disease states, such as recurrent *Clostridium difficile* colitis, however its potential for microbiome stabilization during the course of surgery and recovery is largely unknown. Molecular diplomacy between pathogen and host is possible, however it requires a deeper understanding of the ecological and molecular interactions between the host and the microbiome as well as between the microbes themselves. Only then will it be possible to uncover new therapeutic strategies aimed at preservation of the composition and function of the health-promoting intestinal microbiome and to constrain virulence activation of the potential pathogens through the course of surgical injury.(16,38)

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Key points

1. Health-promoting intestinal microbes are essential modulators of the immune, metabolic and neuroendocrine responses to stress of injury and to surgical recovery
2. Disruption of the intestinal microbiome with surgery and peri-operative treatments, such as antibiotics, lack of enteral nutrition and use of opioid pain medications, have a profound effect on the composition and function of the intestinal microbiome.
3. Problems with post-operative wound healing and wound infections have been directly linked to intestinal microbial dysbiosis.
4. Intestinal bacteria play a central role in the etiopathogenesis of anastomotic leak.
5. A deeper understanding of the ecological and molecular interactions between the host and its microbial counterparts is necessary to develop new therapeutic strategies aimed at preservation of the composition and function of the health-promoting intestinal microbiome and to constrain virulence activation of the potential pathogens through the course of surgical injury.