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Preparing the Bowel for Surgery: Learning from the Past and Planning for the Future

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We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.

TS Eliot

Introduction

In the early 1900s the application of “intestinal antisepsis” prior to gastrointestinal surgery was proposed when surgeons repeatedly observed high rates of mortality following surgery for strangulated small bowel obstruction (1). Recognizing that some form of uncharacterized endogenous toxin was released immediately following reduction of the strangulated bowel, various antiseptics were tested in animals, and subsequently in humans (2, 3). Regimens were applied to a broad range of alimentary tract operations with dramatic improvements in the incidence of postoperative sepsis (4). Surgeons began to vary the choice, route, and timing of antibiotics in clinical trials in the 1970’s (5). Then, using culture-based techniques, microbiologists began to taxonomically characterize the offending microbes and through *in vitro* experiments, were able to identify strategies to eliminate them *in vivo* (6). As complication rates continued to improve into the turn of this millennium, the need to fully prepare the bowel for surgery was questioned and even eliminated by some surgeons (7). However, many surgeons insisted on the original combined bowel preparation that included mechanical cleansing and oral non-absorbable antibiotics. As retrospective analyses emerged to support this historical practice, the use of the mechanical bowel preparation (MBP) with combined oral or intravenous antibiotics has witnessed a resurgence (8).

While surgical site infections (SSIs) and anastomotic leak (AL) rates have remained at a historic lows, the biologic basis by which intestinal antisepsis is protective in one case and not in the others remains unknown. In addition, we have failed to recalibrate our MBP regimen against the rapidly evolving and ever-changing microbiology that now predominates

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in our ever-aging and ever more complex surgical patients (9). Stated differently, while we have observed improved outcomes from empiric interventions, we have failed to determine their precise mechanisms of action. While descriptive clinical trials, retrospective analyses, large data mining efforts, and meta-analyses have appeared and reappeared (10, 11), they all suffer from the same flaw: they lack the basic information needed to understand why certain patients today develop life threatening SSIs and AL. As a result, worldwide, the practice of preparing the bowel prior to intestinal surgery remains highly variable.

In this review, we posit that the principal reason for the ongoing variability in this field is the lacking of foundational science characterizing the changes in the intestinal microbiome that occur through the perioperative period, and which microbiota need to be preserved or neutralized. Although recent advances have demonstrated the beneficial effect of the intestinal microbiome in human health (12), we continue to utilize an indiscriminant “kill strategy” based on fifty year-old science and technology. The purpose of this review is to outline a path to move toward a more robust science-based methodology that will inform our ability to understand, predict, and prevent infectious complications from intestinal surgery.

Historical Perspective

While there are many historical accounts outlining the genesis of the bowel preparation as a method to reduce infection following intestinal surgery, we shall begin with one of the early mentions describing the practice of “intestinal antisepsis”. In the November 4, 1899 issue of the *British Medical Journal*, the article “a discussion on intestinal antiseptics” by Burney Yeo, MD, Senior Physician at King’s College Hospital and Professor of Medicine, revealed the thinking of the period with respect to bowel decontamination (13): “a mixture of benzoates, salicylates, and naphthol; 15 grains of such a mixture, twice daily, is harmless... The proof that this mixture acts as an intestinal antiseptic is given by the rapid deodorization of the solid and gaseous discharges from the bowel. Systematic intestinal irrigation in these cases has also been found a valuable aid to other antiseptic treatment.”

Both purgative cleansing via whole bowel irrigation and intestinal decontamination with available agents were seen as key methods to clear the bowel of its harmful content. In 1919, Lester Dragstedt, an early chair of the department of surgery at the University of Chicago, continued this line of inquiry by attempting to elucidate the cause of death in acute intestinal obstruction. Because they failed to isolate bacteria from the blood in these experiments, he and his colleagues hypothesized that a toxin, either from the intestinal tissues or luminal bacteria, was being released (14). Using a dog model of closed loop obstruction, they demonstrated that washing the intestinal loops with sterile water and ether prevented mortality, and confirmed that the toxic substance was related to the intestinal bacteria, and not the intestinal tissues.

Once antibiotics became available, Poth, Goligher, among others performed seminal experiments using stool cultures and demonstrated how best to clear the bowel of the harmful bacteria that complicate intestinal surgery (15). A major conclusion from these studies as well as those by Nichols in the 1970’s – 1990’s, was that while purgative cleansing agents themselves did not decrease microbial burden, they facilitated the effect of

oral antibiotics to reduce the mucosal concentration of bacteria. Nichols introduced the idea that bacteria remaining on the mucosa should be a target of the bowel preparation, and using electron microscopy and culture, he demonstrated the importance of oral antibiotics over intravenous antibiotics in this regard (16). Virtually simultaneously, surgical investigators from across the Atlantic performed clinical trials and confirmed the superiority of purgative cleansing and oral antibiotics over intravenous antibiotics in reducing clinical infection rates (17). Nonetheless, as mortality rates continued to decrease and preoperative care moved to the outpatient setting, surgeons began to question the need for the MBP. Several large randomized clinical trials were initiated and appeared to confirm that the time was right to abandon MBP (18). Importantly, oral antibiotics were usually eliminated from the treatment arms so the use of bowel preparation was compared to no bowel preparation, in both instances without the administration of concomitant oral antibiotics. In most of these trials, confirmatory cultures were abandoned in favor of basic clinical outcome measures (i.e. surgical site infection, anastomotic leak) (19).

The debate continues among surgeons as to whether oral antibiotics and/or mechanical cleansing is necessary (20). Electronic “data mining” of vast volumes of patient records are generating multiple reports from all over the world, each coming to the same conclusion: the probability of SSIs and ALs following intestinal surgery is significantly reduced when patients undergo MBP with the addition of oral antibiotics (21). It seems today that at the “*end of all our exploring, we have arrived where we started.*”

Towards a new era

There is a growing suggestion that a broad-based “kill strategy” may not be the only method to prevent intestinal bacteria from causing harm following surgery. There is an emerging body of knowledge elucidating the important role of the intestinal microbiome in health and disease. The microbiome of the intestine encompasses the many elements that make up its functional whole, from its community structure, its membership, its genes, and its metabolic products (22). We must now consider intestinal microbes in a context-dependent manner in order to appreciate their behavior, phenotype, and influence on one another (23). Sequencing technology has facilitated a more complete understanding of the intestinal microbiome by not only characterizing the taxonomy of all of the microbes that are present, but also their genomes, phylogeny, community ecology, and their functional effect in remote tissues using metabolomics and proteomics (24). Surprisingly, our predecessors in 1899 understood the importance of this interkingdom harmony (13): “we are still very much in the dark as to the precise mode of action of pathogenic microbes, but we do know that their activities and their virulence vary greatly according to their environment, and that it is *not necessary to kill them in order to make them relatively harmless.*” Virulence, the property of a microbe to express harmfulness against a competing or predatory microorganism or against its host, is dynamically activated by mechanisms such as telesensing of host tissue factors released during physiological stress and by bacterial cell-to-cell communication signaling systems such as quorum sensing (25). Bacteria are constantly gathering, processing, and transducing local environmental cues and deciding whether virulence expression enhances or diminishes their evolutionary fitness (26). This dynamism has led to the Molecular Koch’s Postulates of infection pathogenesis (27), which states that beyond species alone, bacterial phenotype

and the microbial community structure that surrounds it must be understood in order to define the role that a given microbe or microbial community plays in a given disease process (28).

Much of the limitation to move beyond current formulations of bowel preparation regimens lies in the lack of incorporation of the Molecular Koch's Postulates to advance our understanding of the pathogenesis of SSIs and AL. As a result, antibiotics used to prepare the bowel for surgery have not changed in decades despite the recognition that antibiotic resistance is now becoming widespread among surgical patients (29, 30). For example, a recent report from Leeds, United Kingdom, has emphasized the need to recalibrate antibiotic prophylaxis for colon surgery as ever more resistant *Enterobacteriaceae* are found to be responsible for surgical site infections (31). Perhaps the time has come for surgeons to "hold court" and forge the path forward for the rational design of intestinal antisepsis protocols based on new understanding of the evolving microbiology of the alimentary tract in response to surgery (32).

The pathogenesis of SSIs is likely to be more complex than is currently explained

The conventional notion that a wound infection is simply a matter of excessive intraoperative contamination seems to be in need of further examination. Experience with complex and difficult surgical situations and their attendant unpredictability lead one to conclude that much more is at play (33). The aphorism that infection takes place when microbial burden exceeds host clearance capacity does not typically play out in animal models, clinical experience, or clinical studies (34). While this simplistic equation might be able to predict the probability of infection at the extremes of clinical circumstances (i.e. severe immunosuppression, massive contamination), it is not deterministic and fails to be predictive for most of the cases that fall in between.

Here we posit that the final interplay between the ongoing molecular dialogue between a contaminating pathogen and the tissues in which it finds itself is the main predictors that govern the occurrence, course, and outcome of clinical infection. For example, multiple studies demonstrate that many, if not most wounds that are exposed to bacteria during surgery, do not develop clinical infections (35, 36). This is traditionally explained as a simple matter of low microbial burden against the backdrop of a highly vigilant and competent host immune system (37). Yet how and why bacteria in some circumstances seem to "be cleared away" is largely unstudied and therefore remains unknown. Advances in molecular microbiology might explain such a response as the net result of a complex and iterative dialogue between pathogen and host whose final interplay ends in a type of "molecular détente (38)."

Recently performed studies have examined the role of intraoperative bacterial contamination and the development of SSI (39). Many of these studies involved orthopedic prosthesis placements where any resultant infection can be catastrophic. Intraoperative bacterial contamination had no correlation to subsequent clinical infection (40, 41). General surgeons may argue that this is not the case with gastrointestinal surgery where microbial burden and

intraoperative contamination are often high and where most of the pathogens that are associated with SSIs are those that typically colonize the intestinal tract (42). Yet, the evidence that the majority of SSIs are a direct result of the contiguous spread of intestinal organisms into the operative site at the time of surgery remains poorly documented (43). In most gastrointestinal surgery, intraoperative site contamination by intestinal bacteria regularly occurs, yet infection rates remain low (44). Thus, the obvious question: if gut bacteria do not directly contaminate the wound, how else do they get there?

While there is little doubt that excessive intraoperative contamination of intestinal contents can lead to SSIs, their predominant cause in the setting of elective surgery seems less clear. The last fifty years have brought a major decrease in SSIs by virtue of oral and intravenous antibiotic use, improvements in sterile technique, laparoscopic surgery, barrier protection strategies, meticulous attention to operative details, and rigorous enforcement of infection control measures within the operating room environment (45). In aggregate, history suggests that we got it right by implementing the above measures through a process of trial and error. Yet failure to continue to interrogate the mechanisms and efficacy of these measures using next generation technology may explain why serious infections following gastrointestinal surgery still occur.

Here we posit that testing the Trojan Horse hypothesis, which states that blood leukocytes can survey, scavenge, and silently house microbial pathogens from one site, deliver them to a remote site, and cause infection could result in novel SSI prevention strategies (46). Microbes and leukocytes achieve this via interkingdom cooperation whereby microbes within neutrophils/macrophages express an avirulent dormant-like state and host cells tolerate their presence. Microbe-carrying leukocytes can circulate and then home to damaged tissues where they deliver their infectious payload. Delivered microbes are then “cued” by host factors within damaged tissues to express a virulent phenotype and cause clinical infection. Much of the plausibility of this mechanism is a result of the ability of pathogens to turn on and off virulence and alter their phenotype at a moment’s notice in a manner that is highly context dependent. This hypothesis fits well with our long-held intuition and clinical observations that the more trauma to a wound, the greater the likelihood of infection (47).

The ostensible sites where leukocytes scavenge and pick up potential pathogens are at mucosal surfaces, particularly in the gastrointestinal tract due to its high microbial density. Neutrophils and macrophages are in constant contact with the epithelium and have been shown to regularly acquire microbes (48). Although neutrophils and macrophages can be highly tolerant to the presence of various pathogens within their cytoplasm, most of the time, the pathogens are nonetheless eliminated (49, 50). However, prolonged pathogen survival within these cell lines can occur by mechanisms that include both pathogen-induced immunosuppression and host cell tolerance mechanisms. As these cells circulate, otherwise sterile tissues (pancreas, wound, lung) that are now damaged or inflamed become neutrophil “sinks.” This sequence of events could provide a mechanism to explain infected pancreatic necrosis, postoperative pneumonias, and other types of wound infections.

We have experimentally modeled the Trojan Horse mechanism of wound infection in mice using methicillin resistant *Staphylococcus aureus* (MRSA) tagged with a bioluminescent tracer, which we directly inoculated into the gut via oral gavage (51). When mice were then subsequently subjected to a traumatic wound injury (midline laparotomy), bioluminescent MRSA silently traveled from the gut to wound and caused gross clinical infection. Remarkably, these results suggested that neutrophils can indeed pick up pathogens at the gut epithelial surface and deliver them to sites of injured/inflamed tissues remote from the gut. Consideration of the Trojan Horse hypothesis as a plausible mechanism of SSI offers the possibility of applying next generation bowel preparation solutions (i.e bowel prep 2.0) to patients at risk for wound infections beyond operations on the intestinal track itself, can expand their indications and methods of use (52).

The pathogenesis of AL is likely to be more complex than is currently explained

The following letter to the editor was received by the *Journal of Gastroenterology and Hepatology* from the Edinburgh Colorectal Unit, Western General Hospital, Edinburgh, United Kingdom and published in 2007 (53). On reexploration on postoperative 9, the authors noted: “there was no tension on the anastomosis and histological examination of the 10-cm resected segment containing the original anastomosis showed no signs of ischemia. Because the pathophysiology of infection is now better understood, the effects of the toxins on the anastomotic area of the bowel is certainly of concern and may contribute to anastomotic leakage. We accept that the present patient’s anastomotic leak may well have been secondary to a technical factor, but we hope to highlight the potential detrimental effect of postoperative *C. difficile* infection on a colorectal anastomosis.”

While there is little doubt that poor technique certainly *can* cause an anastomotic leak, here we assert that there exists little evidence to support the claim that it is the dominant cause of most leaks in everyday practice (54, 55, 56). Yet in line with the general theme of this review, there exists compelling evidence, beyond the prescient speculation of our colleagues from Edinburgh, that bacteria play a key contributory role in the pathogenesis of anastomotic leak. In fact, solid evidence for this hypothesis has existed for over sixty years. Animal studies were performed in 1954 in which a feeding catheter was inserted just upstream of a devascularized colon segment and infused with daily antibiotics (tetracycline) (57). Results demonstrated that antibiotics reversed the ischemia and prevented leak. A rat study performed in 1984 confirmed these findings and demonstrated that leaks could indeed be eliminated with oral antibiotics but not with intravenous antibiotics of a similar spectrum (58). In 1994, studies performed by Schardey implicated a specific species, *Pseudomonas aeruginosa*, whose introduction to the anastomosis of rats produced leak (59). Multiple studies in humans from 1960 to this day continue to demonstrate that oral non-absorbable antibiotics or protocols of selective digestive decontamination prevent leakage more effectively than the use of intravenous antibiotics alone (60). In 1977, the classic randomized controlled trial to define the role and efficacy of oral antibiotic prophylaxis in colon surgery was published (61). Results demonstrated a clear reduction in infection related complications including SSIs and sepsis. Perhaps unanticipated, the study demonstrated that

anastomotic leak rates were significantly decreased. Further studies as recent as 2015 again confirmed that oral antibiotics prevent anastomotic leaks (62).

Similar to the historical resistance to accept a role for *Helicobacter pylori* in peptic ulcer disease, we may find it difficult to accept that bacteria play a key role in anastomotic leak pathogenesis primarily because bacteria “are there all the time (63).” To remedy this assumption, we must again turn to the Molecular Koch’s Postulates. Accumulating evidence points to both *P. aeruginosa* and *Enterococcus faecalis*, two organisms that are very difficult to eradicate from the intestinal track even when administering the appropriate antibiotics (64). These organisms possess the ability for the *in vivo* production of collagenase, which can break down healing anastomotic tissues. We confirmed that both organisms produce a significant amount of collagenase and postulated that bacterial collagenase, in contrast to host derived collagenases, might play a key and causative role in anastomotic leak (65, 66). However, in order to fulfill the Molecular Koch’s Postulates in the context of an infectious pathogenesis of AL, identification of collagenase producing species of bacteria alone would be insufficient. Several contingencies need to be met (67). First, collagenase producing bacteria would have to be present on anastomotic tissues. Second, they would need to be “activated” *in vivo* to express a significant degree of collagenase that would impair healing. Third, the composition and function of the indigenous microbiome present at anastomotic tissues would have to be disrupted sufficiently to allow these pathogens to gain access to anastomotic tissues. Fourth, the pathogens would have to amplify the tissue inflammatory response following anastomotic surgery to a degree that could be defined as pathoadaptive to normal healing. Finally, as originally outlined in the Molecular Koch’s Postulates paradigm, the genes that regulate collagenase production would need to be deleted (without affecting the growth and presence of the bacteria themselves) and be shown to no longer induce the AL phenotype (68). We performed this very series of experiments in a rat model of anastomotic leak and provided the necessary molecular detail to confirm that two intestinal microbes (*P. aeruginosa*, *E. faecalis*) can fulfill these criteria as primary causative agents in anastomotic leak pathogenesis (65, 66). Most recently we identified yet a third organism capable of causing leak, *Serratia marcescens* (69).

Surgeons understandably continue to take pause and maintain a healthy skepticism. Are there not known risk factors present within the practice of surgery that contribute to leak pathogenesis such as ischemia, blood loss, obesity, smoking, etc (70)? While these factors increase the *probability* of leak, they themselves are not deterministic of leak (see figure 1). Each of these factors has been shown to dramatically affect the composition, function, and phenotype of intestinal microbes (71, 72, 73). Simply stated, leaks develop when the right bacteria (*E. faecalis*, *P. aeruginosa*), with the right virulence genes (collagenase), expressed, *in vivo*, by the right activating cues (long operation, blood loss, difficult dissection, etc), existing within a critically deficient microbiome (history of smoking, alcohol use, preoperative chemo-radiation, antibiotic use), amplify the inflammatory process to a point at which necrosis and dehiscence develop (74). Thus while such “activated” bacteria alone are not *sufficient* to cause leak, they are *necessary* for leaks to occur. As a note of reference, regarding the case study cited at the beginning of this section, we would like to point out that *C. difficile* is known to abundantly produce collagenase (75).

Using microbiome sciences to develop “bowel prep 2.0.”

The debate about how to prepare the bowel prior to major gastrointestinal surgery continues to rely on the above described traditional paradigm (76, 77). Clinical trials still typically lack the molecular and microbiologic detail needed to inform mechanism. Central to the confusion in this debate is the lack of recognition of the importance of the normal microbiota to suppress the pathobiota (colonization resistance) and promote intestinal healing (78). Also in the era of minimally invasive surgery, oral antibiotics may be less important as the microbiota are minimally disturbed and wound trauma/damage is limited (79). Finally, how the normal microbiota “refaunate” following surgery and provide their health promoting effects has never been addressed and is likely to be very important in how they provide resilience to the host during the recovery period (figure 2).

Two recent reviews by experts in the field have analyzed the state of knowledge on bowel preparation regimens (80, 81). While both experts agreed that the evidence favors the combined use of MBP, oral and IV antibiotics, they both observe that level 1 evidence is lacking. Each expert called for a four arm randomized prospective clinical trial in which several arms did not overlap. Were these studies to be carried out with SSI and AL as clinical endpoints, six arms would be required to test all possible variations in regimens and over 3000 patients would be needed. Not only would such proposed trials be cost-prohibitive, but without high resolution microbial analyses, they would be uninformative to the pathogenesis of SSI and AL and would fail to inform how best to prevent them.

The historic notion that as complete as possible of an intestinal decontamination should be the goal of any effective bowel preparation remains at best uncertain. Both at the level of the wound and anastomosis, there is compelling evidence that preservation of the normal microbiota is highly beneficial to healing (49, 82, 83). It seems time that we begin to understand which microbes should be preserved to promote healing and which should be “controlled” rather than eliminated in order to prevent infection (69). As our predecessors predicted about the nature of pathogens whose virulence is conditionally activated, “it is not necessary to kill them in order to make them relatively harmless (13).”

Conclusion

All stakeholders involved in the process of modern surgery including patients, insurance companies, surgeons, and administrators, seek to reduce complications and costs. Today, the most common reason for a hospital readmission following surgery is infection and it is also the most costly (84). As the progress of surgical science continues, it is now time to allow next generation technology in microbial sciences to recalibrate our thinking so that we may realize a more scientifically validated method of preparing the alimentary tract for surgery.

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Figure 1.

Defining the probabilistic from the deterministic in anastomotic leak pathogenesis. (A) Some of the known risk factors associated with anastomotic leak that have been tested for their relative weighted risk on the probability of predicting a leak. The mechanisms of these risk factors is poorly described. (B) A deterministic view of the microbial pathogenesis of anastomotic leak demonstrating the multiple contingencies required for a leak to become clinically manifested. Each of the risk factors have been shown to alter the intestinal microbiome.

Figure 2.

Theoretical framework by which a bowel preparation method might maintain an abundant health-promoting microbiota that can suppress the growth and harmfulness of pathobiota. (A) Rationale for mechanical bowel preparation; (B) potential advantage of no bowel preparation; (C) inadequacy of bowel preparation in the modern era; (D) bowel preparation 2.0. A–D demonstrate that the most efficacious manner in which to prepare the bowel for surgery will require a comprehensive assessment of the intestinal microbiota and the remaining pathobiota. Current accepted methods for bowel preparation dismiss the importance of the normal microbiota in providing colonization resistance to colonizing pathogens. Rates of refaunaion of the normal microbiota after bowel preparation are unstudied and therefore unknown.