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Anastomotic Leak: Toward an Understanding of Its Root Causes

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Abstract

Background—When an anastomotic leak is discussed at a typical surgical morbidity and mortality conference, it is often presented as a due to an error in surgical technique involving ischemia, tension, or device failure. Here we assert that without direct visual analysis of the leak site and its tissue histology, an ex post facto claim that an anastomotic leak is due to an error in surgical technique remains speculative.

Methods—The arguments and rationale used to conclude that an anastomotic leak is due to an error in surgical technique are critically reviewed and assessed for their validity.

Results—No case series or literature exists in which a root cause analysis has been carried out with visual and tissue level evidence to determine the root cause(s) of an anastomotic leak.

Conclusions—At the individual case level, declaring that an anastomotic leak is due to an error in surgical technique without clear and compelling evidence either visually and/or at the tissue level to substantiate such a claim remains speculative.

Introduction

Discussions around the causes of anastomotic leak among surgeons can become quite heated and are impassioned by the idea that there are always two victims of this dreaded complication, the patient and the surgeon.1 No matter who you are or where you trained, an anastomotic leak following elective surgery is invariably internalized as a personal failure.2 Consider the following quote from the book by Bosk 3 “Forgive and Remember” about managing medical errors:

When the patient of an internist dies, the natural question his colleagues ask is, ‘What happened?’ When the patient of a surgeon dies his colleagues ask, ‘What did you do?’

According to conventional wisdom, an anastomotic leak can only have two causes, an error in surgical technique or “patient-related factors.” Framing an anastomotic leak as somehow due to either an error by the surgeon or, most remarkably, attributable to the patient, without

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specific evidence for such, presents a moral hazard.4,5 Those espousing this definition will contend that they are not actually blaming the patient despite the fact that the two most common patient-related factors, smoking 6 and obesity 7, are considered to be a result of the "patient's own doing.8,9 In this piece, we will advance the idea that uncovering potential reasoning errors behind how surgeons attribute causality to anastomotic leaks may be a useful exercise to redirect research to prevent this devastating and disabling complication.

What Evidence Is Needed to Establish the Root Cause of Anastomotic Leak?

When an anastomotic leak is presented at morbidity and mortality conference as an "error in surgical technique," in order to invoke a technical error as causative to the leak, the actual technical error that occurred must be specifically identified. For example, a recent case was presented in which an anastomotic leak occurred following a right hemicolectomy that reportedly proceeded uneventfully during the index operation. During the take-back laparotomy, as the patient developed localized peritonitis, there was a pinhole dehiscence of the anastomotic staple line where the staple lines crossed. Discussion ensued regarding crossing staple lines, the unusually low incidence of anastomotic leaks following right hemicolectomies, and whether a bowel prep was used. The operating surgeon, an experienced high-volume surgeon, remarked that he performed this anastomosis as he has done with all others, none of which leaked. Yet for this particular leak, the trainees left the room with the impression that crossing staple lines are somehow causally linked to the anastomotic leak. As implied here, using this of reasoning fails to account for all of the other right hemicolectomies performed by this surgeon using this very same technique that did not leak. Discussions such as the one above fall into the category of invoking the "between-group comparison fallacy" as has been previously discussed.10 The incongruence of this line of reasoning lies in failing to reconcile differences in outcomes that occur within a treatment group (i.e., within-group differences). For example, consider the following study seeking to define the role of ischemia in anastomotic leak pathogenesis that begins with the opening sentence "Large bowel anastomotic breakdown occurs as a result of perianastomotic ischaemia.11 To prove this assertion, the authors examine antecedent risk factors for microvascular disease including smoking, hypertension, diabetes, and ischemic heart disease that they then correlate to histopathological examination of the resection margin vasculature and anastomotic leak development. As might be expected, smokers and those patients with hypertension had a significant increase in the prevalence of microvascular disease as seen in Fig. 1. Furthermore among those patients that leaked, nearly 80% exhibited small vessel disease implying that ischemia is highly prevalent in leaking patients. Interestingly among the group that did not leak, still 40% exhibited small vessel disease; why did none of these patient leak? The authors conclude "This study emphasizes the importance of the colonic microcirculation in anastomotic healing." This study and others seem to suggest that between-group comparisons and a P value can invoke mechanism of disease. Such comparisons confuse causation with association and suffer from attribution error. Yet the defense of such arguments is always the same: the causes of anastomotic leaks are multifactorial, and here we are just claiming that ischemia is one of the many likely factors.

So what would it take to be able to establish the root cause of an anastomotic leak at the individual case level? To address this, it may be useful to consider the example of a plane crash that results in casualties. In this case, there is a coordinated “root cause” analysis that involves assembling all parts of the airplane in a hanger, convening a team of expert air-crash investigators (FAA) and performing a deliberative analysis via an expert consensus panel to make the best attempt to determine the “root cause” of the crash. This does not exist at a typical morbidity and mortality (M&M) conference when discussing an anastomotic leak. Discussions of ischemia, tension, suture material, device choice, technique, “dog ears,12,13 etc. are voiced by experts coming to no consensus on the actual cause of the leak. Thankfully anastomotic leaks are rare, and preventative measures (mechanical bowel preparations, protective stoma) 14 and rescue protocols (imaging, source control) have improved both the incidence and mortality of this dreaded complication.11 Yet the problem persists and each and every anastomotic leak is disabling and disrupts the implementation of adjuvant chemotherapy, prolongs hospitalization, requires multiple interventions, extends exposure to antibiotics, and carries the sequelae of long-term problems such as dysphagia, low anterior resection syndrome, cancer recurrence, and chronic pain.15,16,17,18

One limitation to uncover the root cause of an anastomotic leak is that, today, most leaks can be managed without re-exploration and therefore leaking tissues cannot be examined directly. For example, performing a root cause analysis of an anastomotic leak, as is done following an air disaster, would require excision of the involved intestinal segment and defining the degree of blood vessel patency/density and performing a layer by layer histologic analysis with staining for bacteria, collagen, immune cellularity, and other parameters of healing. Assembling a series of anastomotic leaks analyzed in this manner might shed some light on the root causes of anastomotic leaks. That we are aware, only one such study has been attempted and involved assessing blood vessel density within anastomotic leak tissues via CD31 immunohistochemical staining.19 Despite the prevailing thought that ischemia is a major contributor of anastomotic leak, results from this study failed to identify ischemia as a cause of leak. In a rat model, a colorectal anastomosis was subjected to segmental ischemia by ligating its feeding blood vessels; no evidence of ischemia was observed when tissues were excised 14 days later.20 In fact, evidence of enhanced neovascularity and angiogenesis was observed in this study. Even if it were possible to examine intestinal tissues postoperatively, it is challenging, if not impossible to account for the time-dependent adaptation of the bowel (i.e., activation of vascular endothelial growth factor-VEGF and blood vessel growth) that occurs following anastomotic construction. 21 Furthermore, even if studies existed in which a “root cause” analysis of excised tissues from anastomotic leaks was performed, without properly matched control samples from tissues in which a leak did not occur, identified factors claimed to be causative of leak would be difficult if not impossible to verify. Obviously such a study cannot be performed. Yet there may be other ways to serially examine and molecularly analyze anastomotic tissues as they heal that is within our reach via endoscopy (vide infra). These obvious gaps in knowledge beg the following question: are we doing all we can to understand, prevent, and treat anastomotic leak?

“Sealing” of an Intestinal Anastomosis as a Key Step to Healing

From perforated peptic ulcers22, perforated appendicitis23, to perforated diverticulitis 24, surgeons are keenly aware that many “leaks” in the gastrointestinal track can naturally seal themselves, remain minimally symptomatic, and even fully heal without treatment. In fact many surgeons argue that all intestinal anastomoses “leak” to some degree; it is just that most seal themselves off and do not become clinically manifest. While the details of this process remain unknown, its plausibility in the context of the many spontaneous perforations in the intestinal track that self-heal may explain not only how an anastomotic leak heals, but also why so many go undetected.25

If we assume that an anastomotic leak begins inside the bowel lumen as some type of inflammation, ulceration, or dehiscence of the anastomotic construction line, as the pathology progresses and becomes transmural, it is expected to elicit a local external reaction attracting adjacent tissue (omentum, bowel, pleura, pericardium, etc.) to become sealed and contained. Historical vignettes such as when Nissen performed the first fundoplication for a peptic ulcer of the esophagus that had penetrated into the pericardium are testament to such a mechanism.26 In an attempt to exploit this natural mechanism of self-sealing, surgeons have historically claimed that a two-layer anastomosis is superior to a single one.27 Similarly, the lack of a serosal layer in the esophagus or rectum has been claimed to be responsible for higher leak rates observed in these sites.28 Use of serosal, omental, and pleural patches has been hypothesized to be able to recapitulate this natural barrier effect with variable successes.29,30 Most recently, wrapping a pancreatico-jejunostomy with the falciform ligament has been proposed as a preventative measure for the common occurrence of leakage at this site 31. Studies of “everted” versus “inverted” anastomotic construction have also had their historical moment in perfecting anastomotic construction, claiming that the mucosa-to-mucosa anastomosis was the most optimal way of preventing “internal factors” from disrupting anastomotic healing. 32,33

In the context of the above discussion, it is interesting that surgeons often speak of tissues as “forgiving,” referring to the process of adaptive healing in the face of the injury imposed on them when cutting, cauterizing, tying knots, or crushing them together with a stapler to the point where bleeding is not visible on the outside or on the inside of the bowel. It is important to recall that growth factors, chemoattractants, cytokines, etc. are activated by the tissue injury itself 34 and that hypoxia/ischemia is the most potent inducer of vascular endothelial growth factor (VEGF) that elicits the growth of new blood vessels within tissues.35 As such, the ability of the anastomotic connection to “self-seal” must be considered in light of the many processes beyond the technical aspects that occur in the operating room.36,37 If indeed all anastomoses leak and somehow seal, it is worth considering how limited our current knowledge is, and will remain, if we continue to focus our attention on anastomotic complications only as they are discovered when symptoms are severe enough to trigger further investigations (i.e., imaging). Here we posit that the time has come to leverage next-generation technology to define the natural history of anastomotic healing, define what is considered normal healing, and identify those parameters that indicate non-healing before it progresses to a symptomatic leak.

Experimental Models of Anastomotic Sealing: Mouse Models Reflect the Clinical Spectrum in Humans

Experimental models of anastomotic leak that recapitulate the spectrum of presentations observed in humans have been recently described.38,39,40,41,42 These models suggest that an anastomotic leak begins from inside the intestine and involves the participation of intestinal bacteria. In the aggregate, these animal models demonstrate that bacteria are "necessary," but alone not sufficient to cause anastomotic leak. While this body of work unambiguously demonstrates that without the presence of certain bacterial strains on anastomotic tissues (i.e., those that produce the tissue destroying enzyme collagenase), leaks do not occur, and it is important to understand that despite bacteria being omnipresent in the anastomotic environment, their virulence is conditionally expressed and requires the activation by local environmental "cues." This concept was modeled in rodents by constructing a colorectal anastomosis and exposing the anastomosis (via enema) to collagenase-producing strains (i.e., *Enterococcus faecalis, Pseudomonas aeruginosa*), commonly present at leak sites in humans.43 When control mice undergo the anastomotic surgery without exposure to collagenolytic bacteria (no bacteria or mutant strains deleted of their ability to produce collagenase), no leak developed.41 In fact, among control mice, independent of who operates or how the anastomosis is constructed, complete healing occurs and rarely if ever are adhesions external to the anastomosis observed (Fig. 2a). Importantly, and relevant to the human condition, as seen in Fig. 2, only 10% of treated mice (i.e., those exposed to collagenolytic bacteria) developed an anastomotic leak that would be considered clinically relevant (i.e., with abscess formation or peritonitis). Also relevant to the human condition is that the majority (>80%) of mice in this model exposed to collagenolytic bacteria developed leaks that were "sealed" by adjacent perianastomotic tissues. That these perianastomotic adhesions represented sealed off anastomotic leaks was determined by removing the adjacent tissue (omentum/small bowel) off the perianastomotic site (Fig. 2AB). Note that in some cases, the small bowel that sealed the anastomotic site appeared partially obstructed (Fig. 2B) as may occur in humans. Importantly, these sealed off and contained leaks at the perianastomotic sites can be identified from within the bowel lumen when the involved intestinal segment is opened up (Fig. 2C–D) similar to what might be able to be endoscopically observed in patients. Taken together, this series of observations suggests that an anastomotic dehiscence requires the presence of collagenolytic bacteria, most of which do not manifest symptoms and become "sealed" on the outside. Extrapolating these data to the human condition begs the following question: have we exhausted all means of understanding and preventing the progression of an anastomotic dehiscence to an anastomotic leak?45

Convincing Clinical Surgeons that Animal Models Produce Actionable Results

A recent consensus statement on animal models of anastomotic leak suggested that due to the heterogeneity of the methods and models used, translation of findings from animals to humans has been limited 46. It is worth noting that it is extremely difficult, if not impossible to make a healthy animal, small or large, develop an anastomotic leak without incurring

some type of gross technical error in a way that would be unacceptable to any operating surgeon. For example, creating gross ischemia or leaving a major gap in an anastomotic construction to cause a leak in an animal model 47 fosters distrust among surgeons given their experience that anastomotic leaks develop in patients following what is perceived to be a technically adequate and secure anastomosis.

Earlier 48,49,50 and more recent studies 34,51,52,53 invoking a more causative role for bacteria in anastomotic leak pathogenesis seem to have raised interest as relevant to the human condition. First of all, both bodies of work perform a technically adequate anastomosis in rats or mice that are free of ischemia and tension and are tested to be "air tight" as would be performed clinically. In each case, the anastomosis is contaminated by clinically relevant pathogenic bacteria that are commonly isolated from a leaking anastomosis (i.e., *E. faecalis, P. aeruginosa*).43 In both cases, anastomotic leaks develop that would be considered clinically relevant (abscess, peritonitis) by clinical surgeons. Most importantly, in the absence of contamination by highly pathogenic (i.e., collagenase producing) bacteria, leaks in these models are rare or do not occur at all. Work from the Alverdy group has indicated that only those strains that contain genes that encode collagenase enzymes and that are in vivo expressed by local environmental cues have the capacity to activate intestinal tissue proteases (MMP9, plasminogen) 34 and cause leak. Taken together, these studies demonstrate that conditions must be present at anastomotic sites (i.e., nutrient depletion, loss of mucus, absence of competing microbiota, presence of opioids, etc.) that trigger collagenolytic pathogens to express the appropriate phenotype necessary to cause a clinically relevant anastomotic leak.54,55 Implicit in this claim is to recognize that the mere presence of collagenolytic bacteria at anastomotic sites alone is not sufficient to cause a leak; rather environmental cues that signal bacteria to express collagenase are needed. Thus the proper scientific conclusion "collagenolytic bacteria are necessary but alone not sufficient" to cause leak is made based on data from this series of studies.

One often overlooked aspect of animal models that makes creating an anastomotic leak so difficult is that healthy mice, rats, pigs, or dogs do not harbor the same pathogens in their gastrointestinal tract as humans. Most animals used in these models consume a plant-based, high-fiber low-fat diet which creates a diverse and abundant microbiome making colonization by human pathogens, in particular collagenolytic pathogens, very difficult, if not impossible.44 In addition, animals, unlike humans, are not exposed to multiple antibiotics over their lifetime, they do not consume typical low-fiber high-fat western diets as humans, they are not exposed to preoperative chemoradiation and invasive endoscopy, and, perhaps most importantly, they do not harbor cancer—which has now been demonstrated to be associated with a highly pathogenic microbiome.56 It seems that experienced clinical surgeons must be convinced that something beyond technique is making anastomotic surgery "less forgiving" in their patients to explain the unexpected, albeit rare, occurrence of anastomotic leaks that continues to plague their practices. Surgeons are eager to understand the "patient-related factors" that seem to be at play when a technically well done anastomosis results in a leak.45

Western Diet Impairs the Gut Microbiome's Ability to Make Tissues More "Forgiving"

Just like a wound infection cannot occur without the presence of bacteria, converging lines of evidence demonstrate that an anastomotic leak cannot occur without bacteria contaminating the anastomotic site.40,41 While, to many, this may seem paradoxical given that bacteria are always present throughout the intestinal track, it is important to recall that studies suggest that only those intestinal bacteria with the capacity to produce collagenase and that become in vivo expressed to activate intestinal tissue proteases (MMP9, plasminogen) play a key and causative role in the development of anastomotic leak.34,41,53 Yet for such tissue-destroying pathogens to predominate on anastomotic tissues, they must be able to colonize against the "home field advantage" of the normal protective gut microbiota.57 The extent to which factors that disrupt normal protective microbiome in surgical patients including prior antibiotic use, neoadjuvant chemoradiation, poor diet, and exposure to the hospital environment may create opportunism for these pathogens to colonize healing anastomotic tissues.58

Among the many factors that may be important in understanding "microbiome readiness for surgery" is the consumption of a western diet. 59,60,61 For example, we recently demonstrated that 6 weeks of consumption of a western diet (high fat low fiber) in our mouse model of microbe-mediated anastomotic leak shifts the incidence of a clinically relevant anastomotic leak in this model (i.e., abscess formation/peritonitis) from 10 to 50%.44 Most importantly, this elevated incidence can be mitigated by simply feeding mice their standard chow diet just 2 days before the anastomotic surgery which reverses the disruption that a western diet imposes on the gut microbiome.44 Mouse chow is a plant-based high-fiber low-fat diet that renders the mouse microbiome highly resistant to invasion by transient pathogens. The rapidity with which a plant-based high-fiber low-fat diet can reverse the effects of chronic western diet consumption on the microbiome is a finding that may be applicable to patients whereby a program of dietary prehabilitation may be considered for patients undergoing high-risk anastomotic surgery.61

The False Promise of Glues, Sealants, and Devices: Leaks Are Not a Problem of Physics They Are a Problem of Biology

Although the above discussion makes the case that an anastomotic leak may begin as an anastomotic dehiscence whose pathogenesis requires the participation of highly tissue-destructive bacteria, attempts to apply a mechanical solution to the problem persist. Although several trials of glues and sealants placed externally about the anastomosis (Fig. 3A) have failed in clinical trials to prevent anastomotic leaks, 62 this approach continues to be pursued.63 Similarly a recent trial of an internal "stent" to prevent leak failed in a clinical trial (see Fig. 3B).64 There are two conceptual flaws in these approaches that may explain their failure. In the first case, external sealants are not only subject to degradation by tissue and bacteria enzymes, but they also physically distance adjacent tissues from the anastomotic line potentially preventing the external sealing process 65. Internal devices such as the C-seal (Fig. 3B) that attach a condom-like device to the anastomosis place a prosthetic

material onto the anastomotic wound providing a “niche” to which bacteria can adhere. This device also creates the “greenhouse effect” by placing a sheet of material against the anastomotic line allowing humidity and bacteria to be trapped thus promoting their growth and virulence. While these approaches “make sense” from the standpoint of considering anastomotic leak as a problem of physics, they fail when anastomotic leak is considered a problem of biology.

Hypoxia, Ischemia, and Blood Flow: Are Results of Studies Using In Vivo Assessments of Blood Flow (i.e., Indocyanine Green) Proof that Ischemia Plays a Role in Anastomotic Leak?

Randomized trials and meta-analyses have recently made a case for routine use of intraoperative assessment of intestinal blood flow using indocyanine green injection and either external or internal (endoscopic) visual evaluation of perfusion.66,67,68 There are two main issues with this approach that may explain its lack of widespread use. The first is that studies comparing its use versus its non-use correlated to anastomotic leak suffer from the “between-group comparison fallacy” as outlined above.10 The fact that in all studies most patients in the non-use group in fact did not develop an anastomotic leak indicating that if blood flow is a major factor in anastomotic leak, why is its incidence so low when ICG technology is not used? Similarly, among those patients in whom ICG technology is used, why did some patients go on to leak in the treatment group? Proponents may counter: “blood flow is just one aspect of the mechanism by which an anastomosis leaks.” Yet this response is inadequate in the context of trying to reconcile the within-group differences and invoke blood flow as a mechanism of anastomotic leak pathogenesis. The second issue with ICG technology is that in all cases of its use, the anastomotic ring itself (see Fig. 4, next page) remains ischemic despite the fact that leaks occur at the anastomotic ring itself. While it may be argued that it is the blood flow above and below this site that is being assessed that is mechanistically important in ischemia-mediated leak pathogenesis, unfortunately, to date, there has been no evidence, to support this claim. How all of the physiological variables present during general anesthesia are accounted for when only a single measurement of intestinal blood flow is assessed to determine perfusion at a time when the abdomen is either open and exposed to the ambient environment or during laparoscopy when there is 15 cm of H_20 or so of intrabdominal pressure collapsing the vasculature remains unknown. Finally, it needs to be recognized that most episodes of hypotension and hypoxia occur postoperatively,69,70,71 not intraoperatively, which begs the question of whether limiting the use of this technology to a single intraoperative measurement is sufficient to reduce the risk of anastomotic hypoxia. While certainly there is no objection to using this technique as an aid to anastomotic construction, before it can be claimed that its use provides evidence for ischemia as a cause of anastomotic leak, further work is needed.

The Role of Serial Endoscopic Surveillance (SES) with Anastomotic Tissue Analyses to Inform the Path Forward to Reduce/Eliminate Anastomotic Dehiscence and Leak

It is unfortunate that at this point in our surgical history, we have not yet defined the natural history of anastomotic healing in humans. If indeed ischemia may play some role in anastomotic leakage and if it occurs primarily in the postoperative period during episodes of hypotension and hypoxia, then it seems incumbent upon us to devise a method to examine anastomotic tissues directly as they heal. Such an approach may lend itself to more directly detect an anastomotic dehiscence before it becomes a leak and allow for early intervention. Also, bacteria that elude the current “one-size-fits-all” approach of antibiotic prophylaxis may be both detected and potentially eliminated via local decontamination with topical antimicrobials as has been recently described72 Finally given that endoscopic ultrasound has been described to detect the progress of a dehiscence to a leak, 73 its use may trigger early interventions such as placement of clips, sponges, etc. In the aggregate, these approaches may reduce the use of the routine protective stoma in cases of low colorectal anastomotic surgery. Studies have already established that immediate postoperative serial endoscopy (of the esophagus and colorectal anastomotic area) is safe and can detect anastomotic problems before they become they elicit clinical symptoms.74 We have recently published a preliminary report on the feasibility and patient acceptance of serial endoscopic surveillance (SES) and anastomotic lavage and retrieval of samples and demonstrated excellent patient acceptance and the ability to perform molecular analyses on anastomotic lavage samples.75 Perhaps the time has come to deploy the many tools already available to us to understand anastomotic leak pathogenesis at its most fundamental molecular level with the goal of eliminating this devastating and disabling complication.

The Path Forward

Here we assert that the current approach of “wait and watch” for gross clinical signs of leak following high-risk anastomotic surgery such as those occurring in the esophagus and rectum, sites easily reachable by endoscopy, should be reconsidered. The path forward will require proper analysis of all factors involved in anastomotic healing, be they technical or molecular. The challenges of this approach are many: costs, patient acceptance, surgeons’ willingness to endoscope patients with a fresh anastomosis, insurance reimbursement, etc. Perhaps the biggest challenge is overcoming the approach of only examining gross clinical endpoints of anastomotic leak (i.e., pain, fever, CT scan) while varying practice (i.e., antibiotic choice, purgative cleansing) in lieu of identifying the molecular determinants of healing by direct anastomotic inspection and tissue analysis (by anastomotic lavage), determining the true incidence of non-healing (even in those patents without symptoms), and performing a high resolution readout of the perianastomotic microbiome. Given the emerging role of the microbiome in anastomotic leak pathogenesis and given that major role of diet in shaping the resilience of the microbiome, randomized trials of dietary prehabilitation should be considered along with 61 a molecular understanding of its effect on the microbiome 10 and its effect on anastomotic healing, the challenge of which will require direct inspection of the anastomosis while it heals beyond the confines of the

operating room. Only in this manner can we individualize protective measures to our patients as well as tailor our antimicrobial prophylaxis 76. Finally considering non-antibiotic approaches to contain and neutralize the virulence of pathogens among the microbiome without eliminating it altogether should be considered (see Fig. 5). In summary, we propose that a more holistic approach to tracking, understanding, and preventing anastomotic leak is within our reach.

Conclusion

It is important here to clearly state that we recognize that an anastomotic leak certainly can be due to an "error in surgical technique" such as when surgical misconstruction or device failure occurs or when an excessive ischemia is present. Yet to state ex post facto, that such technical factors are *the cause* of an individual anastomotic leak without proper tissue level evidence is counterproductive to advancing our understanding of the root causes of anastomotic leak. The fact that today leaks still occur despite improvements in technique, powerful antibiotics, and expert surgeons working in high-volume centers should force a reconsideration of how we discuss, critically analyze, and draw conclusion regarding their root causes. In addition, given the emerging role of the microbiome in human health and disease, considering how bacteria may be causative agents in the pathogenesis of leak is now critically important. Perhaps, the first step in this process is to challenge pervasive dogma and use all available methods and tools, to define, at the most detailed molecular level possible, how it is that this devastating and costly complication continues to occur and why its precise mechanism of occurrence continues to elude us.

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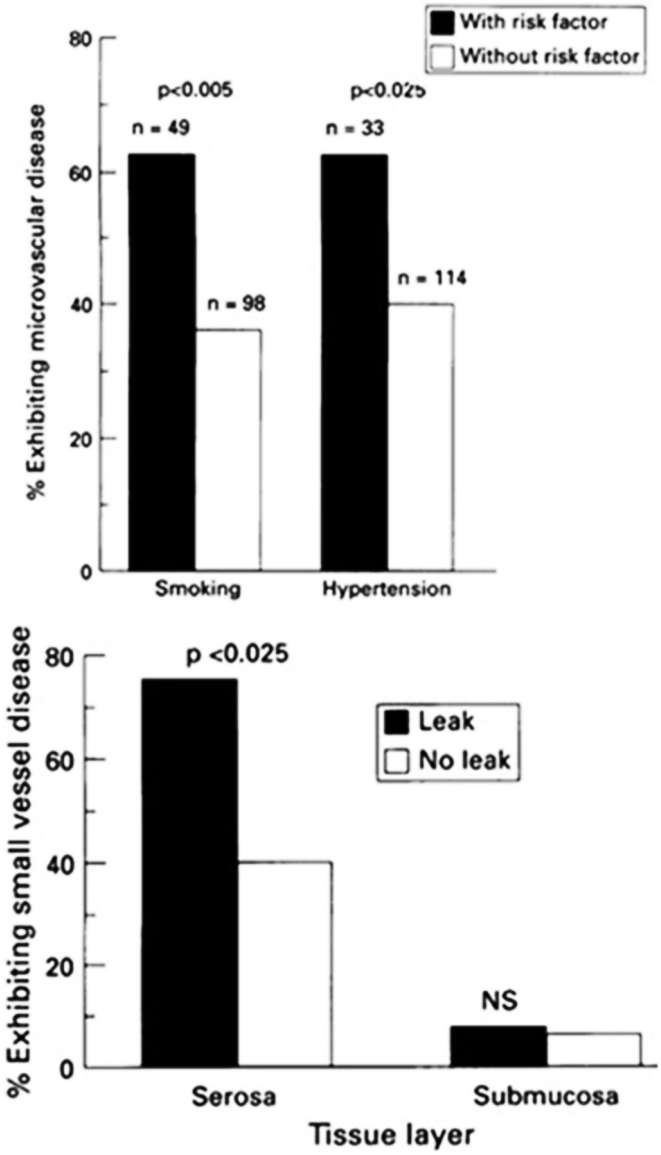

Fig 1.

Presence of microvascular disease at time of anastomotic construction and its association with leak. Upper panel: Even patients without risk factors (smoking, hypertension, etc.) had microvascular disease. Lower panel: Despite 40% of patients exhibiting microvascular disease, none of them leaked.

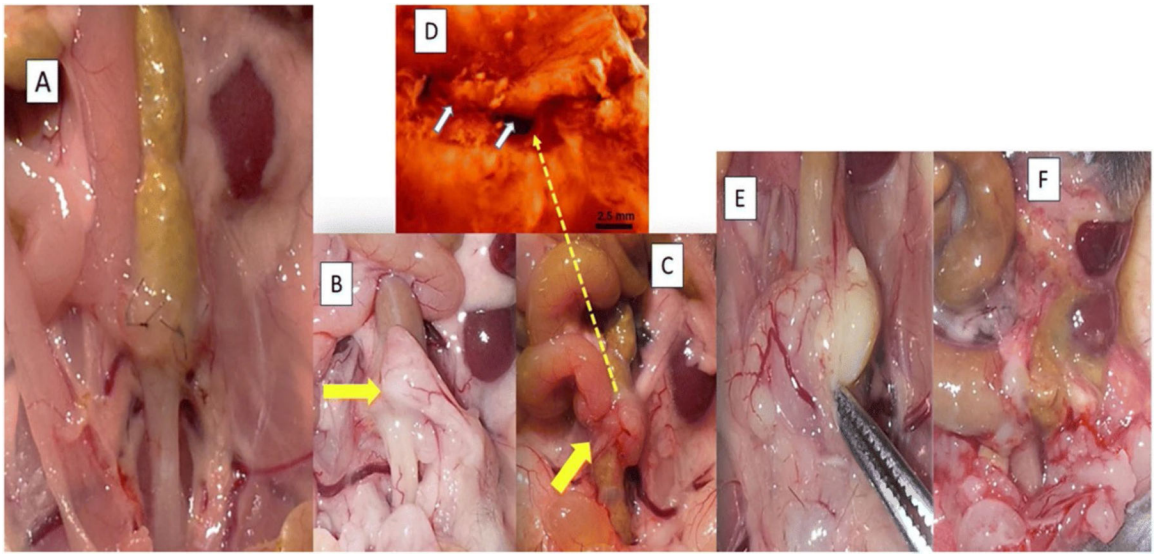

Fig 2.

Images from mouse models of anastomotic leak taken at time of sacrifice. A Untreated control mouse. Anastomosis constructed with interrupted 8–0 proline suture. No evidence of leak, no evidence of adhesions to adjacent structures. B and C Anastomosis constructed with same technique as A; however, anastomosis colonized by high collagenase-producing microbes (Enterococcus faecalis) with tissues expressing high protease activity (MMP9). B A subclinical anastomotic leak that is “sealed” by omentum that has become adherent to the site of the anastomotic dehiscence confirmed by separating the omentum from the anastomotic line. C Solid arrow point to a “sealing effect” in which the small bowel has adhered to the anastomotic junction which grossly appears intact; yet when the small bowel is pulled away, a hole in the anastomosis is visualized (as indicated by dotted yellow arrow in D). Note: the small bowel is partially obstructed and the mouse is asymptomatic. E A perianastomotic abscess from a leak and F Gross peritonitis with inflammatory nodules throughout the peritoneum. Note: abscess formation and peritonitis (E and F) occur in only 10% of mice consuming a normal diet of chow; however, when mice are exposed to the experimental conditions of a western diet, antibiotics, and introduction of collagenolytic bacteria to the anastomosis via enema, abscess formation and peritonitis rates increase to 50% (see reference 44).

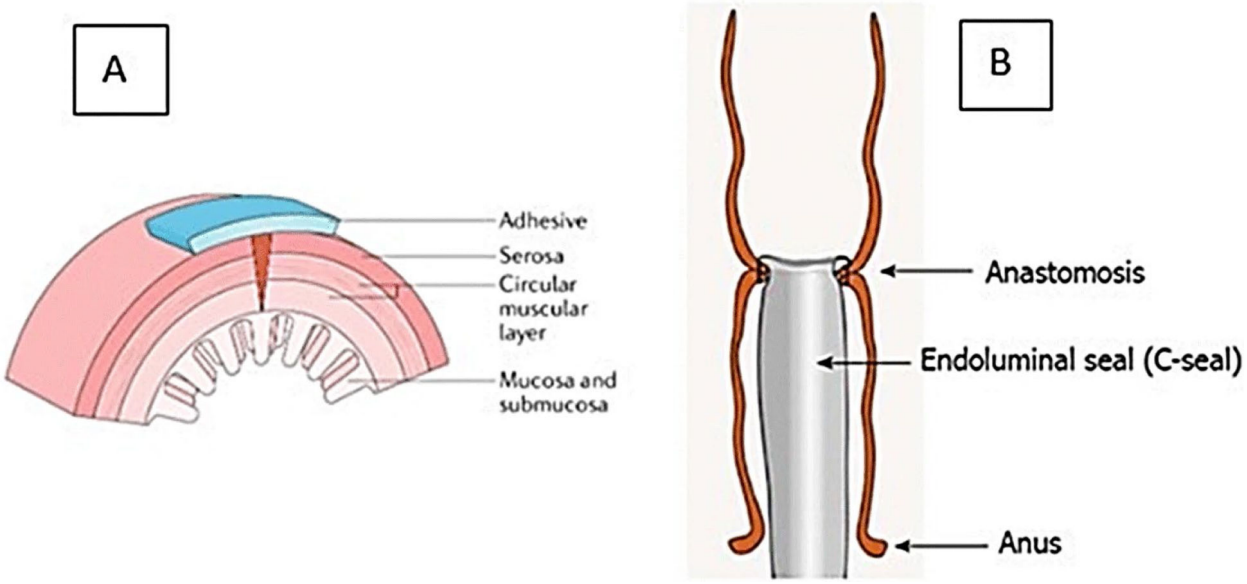

Fig 3.

External and internal reinforcement approaches to prevent anastomotic leak. A Glues applied externally to “seal” anastomotic wounds. B Internal stent affixed to anastomotic line.

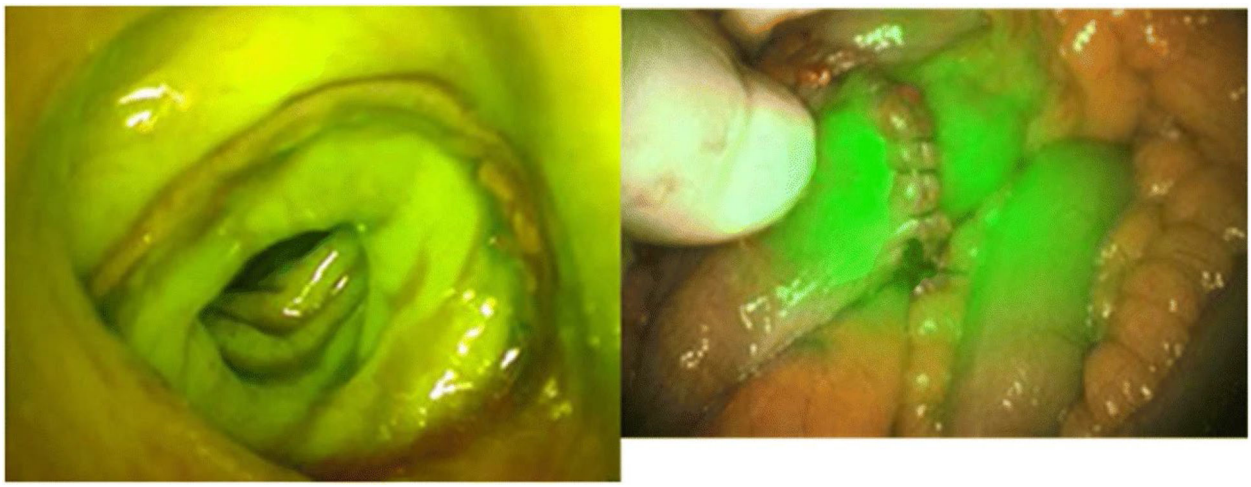

Fig 4.

Indocyanine green in vivo imaging of perfusion indicating that the anastomotic line itself, either in a circular stapled end-to-end anastomosis (EEA) or hand-sewn, fails to appear perfused.

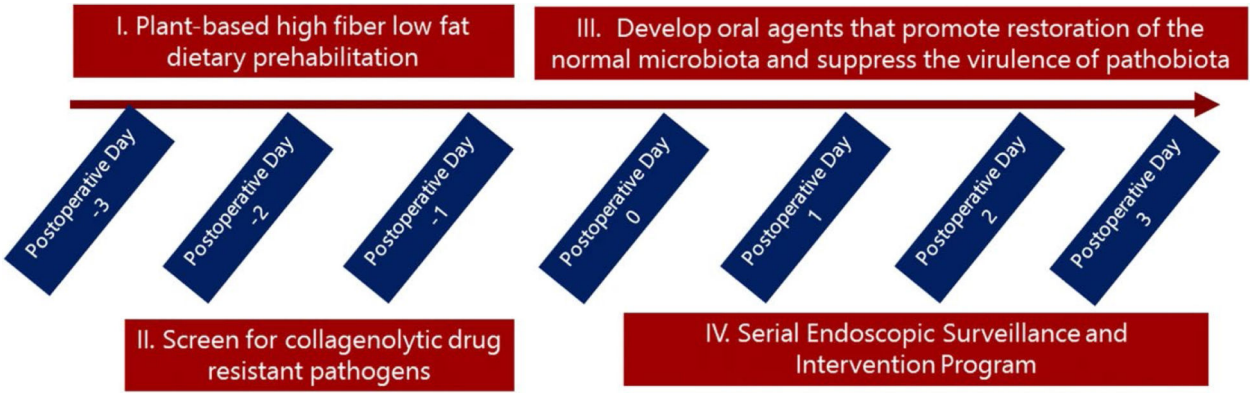

Fig 5.

Preoperative, intraoperative, and postoperative program to prevent and detect anastomotic complications. While many factors may lead to the development of an anastomotic leak, evidence suggests that without bacteria, leaks do not occur. Therefore targeting the mechanisms by which bacteria are involved in the pathogenesis of leak must begin preoperatively by first assessing the “readiness” of the microbiome for surgery by screening for pathogenic bacteria while at the same time providing a prehabilitation diet and postoperative agents that can form a more health-promoting microbiome. Finally, serial endoscopic surveillance can not only help identify those pathogens present on anastomotic sites as they heal, but can also identify areas of developing dehiscences that may be treatable with topical antibiotics or endoscopic interventions (clips, cautery, etc.)