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Prevention of Perioperative Anastomotic Healing Complications: Anastomotic Stricture and Anastomotic Leak

Kristina L. Guyton, M.D.,
Department of Surgery, University of Chicago

Neil H. Hyman, M.D., FACS, FASCRS, and
Department of Surgery, University of Chicago

John C. Alverdy, M.D., FACS
Department of Surgery, University of Chicago

Synopsis

The anastomotic healing complications of postoperative leak and stricture continue to plague surgeons despite many broadly targeted interventions. Evaluation of preventive measure efficacy is difficult due to inconsistent definitions and reporting of these complications. Few interventions have been shown to impact rates of leakage or stricture. However, new evidence is emerging that the intestinal microbiota can play an important role in the development of anastomotic complications. A more holistic approach to understanding the mechanisms of anastomotic complications is needed in order to develop tailored interventions to reduce their frequency. Such an approach may require a more complete definition of the role of the microbiota in anastomotic healing.

Keywords

anastomotic complications; anastomotic healing; anastomotic stricture; anastomotic leak; diverting ileostomy; leak test; mechanical bowel preparation

Anastomotic Complications: A Spectrum of Clinical Presentations

Anastomotic complications encompass a wide variety of clinical manifestations ranging from bleeding and stricture to leakage and perforation. Patients may exhibit a broad spectrum of symptoms that can present acutely, in a delayed fashion, or chronically. Anastomotic leakage may present acutely as septic shock or with much less severe symptoms such as vague discomfort or ileus.[1] Emerging technology has allowed many of the most feared complications of anastomotic surgery, including bleeding and leakage, to be

Corresponding Author: John Alverdy (jalverdy@surgery.bsd.uchicago.edu), **Institution:** The University of Chicago Medicine, 5841 S. Maryland Avenue, MC 5095, Chicago, IL 60637, Office Phone (773) 834-2124, Office Fax (773) 834-1995.

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detected early and often to be treated without surgery.[2,3] For example, anastomotic bleeding frequently can be treated with endoscopic clipping or cauterization when the anastomotic site is within the reach of the endoscope.[2] Yet anastomotic complications can be severe and can lead to disability and occasionally death[4]. In order to understand how to prevent anastomotic complications, an evidence-based approach grounded both on an understanding of the pathophysiology and on clinical trials that demonstrate efficacy is needed. This review will focus on two complications: anastomotic stricture and anastomotic leak. Although there is much dogma passed on from generation to generation regarding how to prevent anastomotic complications, the fact remains that even among high-volume surgeons working in high-volume centers, anastomotic strictures and leaks continue to occur, often with devastating or disabling consequences.

Beyond Tension and Ischemia: While Physics is Important, Biology is a Major Factor in Anastomotic Healing

The classic question asked during morbidity and mortality conference on an anastomotic healing complication is, “Was the anastomosis ischemic or under tension?” No surgeon would willingly leave the operating room with a grossly ischemic anastomosis or with an anastomosis under tension. Yet anastomotic leaks still occur following technically well-constructed anastomoses. This prompts the question of the technique used. Since the turn of the century, surgeons have evaluated multiple technical aspects of anastomotic surgery: everting versus inverting, suture types, one layer versus two layer technique, and hand sewing versus stapling.[5] Collectively, these studies have failed to demonstrate significant differences in effectiveness.[6] Most surgeons would agree that the specific technique used, assuming the methods adhere to good surgical principles, is rarely the determinant of optimum healing. Even well-perfused, well-constructed anastomoses under no tension can develop a leak or stricture; despite surgeons’ belief in their own predictive capacities, clinical studies demonstrate that surgeons cannot predict which anastomoses will leak.[7] In the aggregate, studies reveal that while meticulous attention to the tenets of good surgical practice are important and should be rigorously adhered to, some factors that significantly impact anastomotic healing are not fully understood.

Over the past several decades, a primary focus on using engineering principles to reduce complications has driven device improvement and compound development (e.g., glues or seam bindings) to promote healing. However, most of these studies are decoupled from the biologic factors that underlie the pathophysiology. Despite iterative improvements in technology, application of these innovations has had little impact on anastomotic stricture and leak rates. Focusing research on the pathobiology of anastomotic complications at the cellular and molecular level will lead to new insights and solutions for these problematic healing complications.

Current Understanding: We Have Probabilistic Measurements and We Now Need Deterministic Analyses

Fortunately for patients and physicians, both anastomotic stricture and anastomotic leak are relatively low incidence events. Because of this, it is difficult to study anastomotic complications and to evaluate preventive measures and their clinical efficacy. A plethora of studies have examined the incidence and risk factors for both stricture and leak; however, few studies explore the biologic underpinnings of these phenomena. Additional retrospective studies and speculative conclusions will not bring us closer to understanding and eliminating these postoperative healing complications because the studies merely demonstrate associations, not the causal mechanism. More basic investigative work using next-generation technology and molecular analysis is needed.

Anastomotic Stricture

Retrospective analyses examining anastomotic stricture often focus on the incidence, symptomatic presentation, and subsequent management of the complication itself. There is little understanding of the normal process of intestinal healing and how it becomes altered to lead to stricture formation. This leaves the clinician wondering why, when the same technique is used, one patient's anastomosis strictures but that of another patient heals without incident. There have been numerous proposed reasons for why anastomoses constrict: ischemia, tension, subacute obstruction, circular staplers, narrow diameter staplers, and the occurrence of an anastomotic leak.[8] Few studies have shed light on why anastomotic strictures occur; they have neglected to include factors outside of the technique and conduct of the operation. The intestinal tract is a complex organ made up of epithelial cells, immune cells, stromal cells, and microbial organisms whose number exceeds the total quantity of human cells. A more holistic understanding of the entire host-microbe interaction throughout the course of surgery and healing is essential to elucidate the pathobiology of both anastomotic leak and stricture. One major obstacle has been the lack of access to observe, sample, and analyze an anastomosis as it heals. If we are to advance our understanding of anastomotic healing, future studies need to be designed that can directly examine and sample anastomotic tissues in humans as they heal.

Anastomotic Leak

Clinical studies evaluating causes of anastomotic leak have relied on retrospective analyses that determine associated risk factors. Such studies yield recurring themes generalizable to most complications following surgery, such as poor nutritional status, comorbid diseases, smoking, immunosuppression, advanced tumor grade, hypotension, and blood loss/transfusion.[6,9,10] Studies of the two anatomic regions with the highest anastomotic leak occurrence, the esophagus and rectum, often identify anatomic and physiologic risk factors for leak such as tension, ischemia, and location of the anastomosis.[11,12] However, even in the most carefully conducted multivariate analyses, identified risk factors fall short of explaining why the majority (>75%) of patients with identified risk factors do ***not*** leak. Anastomotic leakage is generally a low frequency event, with approximately 10–15% incidence in the esophagus and rectum and 5–10% elsewhere.[1,13] The rate of leak has

remained largely unchanged over the past twenty-five years. Risk factor analyses may indicate the probability of leak but do not allow us to determine how a given factor contributes to leak pathogenesis. In many cases even the risk factor calculations fall short of identifying the degree of contribution to leak. For example, if smoking, blood loss, and a low rectal anastomosis all significantly contribute to leak, there is little explanation as to why the majority of low rectal anastomoses in smokers subjected to major blood loss do not leak. Adherence to this theoretical framework has led to the perpetual generation of retrospective analyses both confirming and invalidating various risk factors associated with anastomotic leak. Retrospective reviews have neither advanced our understanding of the pathophysiology nor decreased the overall incidence. Though numerous potential risk factors may contribute to leak, the mechanisms by which they contribute and the pathogenesis of anastomotic leak remain poorly understood and need to be properly studied. Even within preclinical models, potential innovations and methods of preventing anastomotic leak are not being effectively evaluated.[14,15] While interventional studies may provide clinically meaningful and statistically significant evidence for potential mechanisms of anastomotic leak, the conclusions of many of these studies are weakened by the lack of a precise definition of anastomotic leak.

The Challenge of Defining Anastomotic Healing Complications

Anastomotic Stricture

The significance of anastomotic stricture varies highly based on the anatomic location of the stricture and the degree of luminal obstruction. While high-grade strictures are immediately recognized due to patient symptoms, low-grade strictures may go completely unidentified. The clinical presentations are also varied in the timing of symptom development following surgery. Early onset obstruction is often attributed to technical error or tissue edema; delayed onset obstruction and stricture formation is felt to be related to chronic inflammation. One of the identified risk factors for stricture includes anastomotic leak, but how this situation differs from a stricture that forms outside of the setting of a leak is unknown[16]. Again, because there are no studies that have defined the natural history of anastomotic healing in real time by directly examining anastomotic tissues over the course of healing (i.e., endoscopy, fluid sampling), much of the pathogenesis of stricture formation remains speculative. In addition because stricture formation is only addressed when there are gross symptoms of obstruction, the technical and physiologic factors that govern its occurrence and outcome remain unknown. Finally, most endoscopic studies in which the anastomosis can be reached and dilated, have not attempted to classify strictures in a defined way that might advance our understanding of their pathogenesis and their response to treatment.

Anastomotic Leak

Conceptually, anastomotic leak is a single entity: the breakdown or insufficiency of the anastomotic line resulting in spillage of intestinal contents outside of the bowel lumen. However, this physical event may have a variety of anatomic consequences that range from a contained abscess that spontaneously resolves to free spillage into the peritoneal cavity. The clinical manifestations mimic this wide variation: no symptoms, ileus, pain, fever, or fatal sepsis.[1] Given the increasing utilization of low colorectal anastomoses, there is an increased

focus on the incidence and pathophysiology of anastomotic leak in this area. Depending on the study and the definition of anastomotic leak used, the observed incidence of colorectal leak varies from almost zero to a third of low colorectal anastomoses.[1,17] Some studies define leak as extravasation of rectally administered contrast identified on radiographic imaging, while others include perianastomotic abscesses identified on CT scan, and still others only include patients who exhibit specific symptoms. Literature reviews have found over forty definitions for anastomotic leak in 107 publications.[18] Inconsistencies in definitions of leak among these studies lead to further challenges in comparing and analyzing the results and in reaching meaningful conclusions[19]. Several methods of classification have been proposed to eliminate the variation in definitions, some based on imaging findings and others based on required intervention (see Table 1).[1] To adequately monitor and evaluate preventive interventions, we need to develop a consistent method of defining and classifying anastomotic complications.

Specific Interventions to Prevent Anastomotic Healing Complications

Anastomotic Stricture

In recent years randomized control studies that directly compare anastomotic technique have been largely abandoned given the perception that the technique itself (hand sewing, circular versus linear stapler, one layer versus two layer) is not a likely factor involved in leak assuming that good surgical principles are followed. The one exception to this generalization has been the stricture rate with staplers. Circular staplers are reported to have higher stricture rates compared to linear stapling.[20,21] Why this occurs has not yet been addressed in any scientific way. While there have been multiple speculations using physics and mathematics to explain this observation, little biology has been applied in experimentation. With circular stapling, a granulation ‘membrane’ often develops that is soft and easy to dilate endoscopically. The smaller the circular diameter of the stapler, the greater the likelihood becomes that this granulation membrane will cause symptoms. As such, it is generally practiced that, to the degree that the bowel lumen allows, larger circular staplers are used, resulting in lower risk of symptomatic stricture. It is not known why linear staplers do not form strictures at similar rates as circular staplers. The pathophysiology of stricture formation has been assumed to be local inflammation that results in collagen overproduction and poor bowel wall remodeling. While multiple engineering-based explanations have been offered, there is no credible evidence that these factors are indeed mechanistically causative.[22] Again, a more holistic understanding of stricture formation will require detailed, dynamic studies of anastomotic healing via direct examination with tissue sampling and analysis. To date there has been little enthusiasm for such an approach, as it is perceived to be excessively risky.

Anastomotic Leak: hand sewn versus stapling, intraoperative evaluation, and diverting ileostomy

In construction of gastrointestinal anastomoses, it is very important to adhere to the tenets of good surgical practice: optimizing the patient preoperatively, avoiding tension, and ensuring adequate blood supply to the healing anastomosis. Yet even the most conscientious and technically proficient surgeons occasionally experience the complication of an anastomotic

leak and its occurrence is most often not anticipated[7]. There is a longstanding debate regarding the superiority of stapled versus hand-sewn anastomoses. For ileocolic anastomoses, a recent Cochrane review suggests that non-diverted stapled anastomoses have a lower anastomotic leak rate as compared to hand sewn anastomoses.[23] However, in difficult to access regions of intestinal tract, such as the esophagus and the rectum, there remains significant debate. For colorectal anastomoses, there is not enough evidence to determine superiority of one method over the other.[24] In the construction of esophageal anastomoses, the numerous methods used to create the connection—stapled, hand sewn, cervical, intrathoracic, end-to-end, side-to-side—have made it difficult to determine superiority of one technique over the other; however, there has been a recent trend toward a side-to-side linearly stapled technique.[25,26]

Intraoperative evaluation, known as a “leak test,” is commonly performed following creation of esophageal, gastric, and rectal anastomoses, where the anastomosis is proximal or distal enough in the bowel to be accessible by endoscopy. The anastomosis is examined for staple line bleeding or gross abnormalities, and the integrity of the anastomosis is tested by examining for bubbles escaping from the insufflated lumen as the bowel is submerged in liquid. Studies have demonstrated that intraoperative endoscopic assessment of the anastomotic line is safe, feasible and can identify gross bleeding and abnormalities. Recent studies suggest that this method may reduce anastomotic complications and no studies have shown any harm in performing the procedure.[27–29]

In colorectal anastomoses, many surgeons choose to perform a diverting ileostomy. While it is known that this procedure and its subsequent reversal carry the independent risks of morbidity and add costs, the impact that diversion has on prevention of anastomotic leak remains unclear.[30–32] The theory behind fecal diversion is that it eliminates the anastomotic stress of bowel wall dilation during healing and that any leakage that occurs has less severe consequences by avoiding large volume fecal spillage. The question remains, does fecal diversion have any impact on prevention of anastomotic leak, or does it simply minimize the severity of the leak? A meta-analysis of randomized controlled trials examining this issue concluded that defunctioning stomas decrease the leak rate as defined by clinical symptoms such as peritonitis, pelvic abscess, rectovaginal fistula, or fecal discharge from a drain; radiologically demonstrated leakage without these clinical sequelae was not included in the analysis.[33] This study and similar studies are plagued by the recurrent issue of lack of a standardized definition of anastomotic leak. If a diverting stoma serves to decrease the severity of leak, many clinically evident leaks may then be only categorized as radiologically detectible leaks, leading to the false conclusion that fecal diversion decreases anastomotic leak rate.

The Biology of Anastomotic Healing

A great deal is known about healing of the external skin after injury, but much less is known about intestinal healing. This is due to the easy accessibility of the skin as it heals as opposed to the intestinal mucosa. The gastrointestinal tract wall is composed of the surrounding serosa; the smooth muscle-containing muscularis propria; the collagen-containing submucosa providing tensile strength; and the epithelial mucosa and mucous

layer that provide the interface with and barrier to the luminal contents. Most importantly the intestinal mucosa heals in close contact with the intestinal microbiota, the densest biomass in the body. The process of intestinal healing is characterized by the three phases of inflammation, proliferation, and remodeling. The greatest risk to the anastomosis is thought to occur during the inflammatory phase when collagen proteolytic activity is greatest. After forty-eight hours, the strength in esophageal anastomoses decreases by almost 40%, while colonic anastomoses lose 70% of their initial strength. These strengths gradually increase as fibroblasts and smooth muscle cells synthesize new collagen while the wound is remodeled.[34,35] Disorders of this process may contribute to the development of anastomotic stricture and anastomotic leak. It is known that local inflammation impairs wound healing by prolonging the inflammatory phase and increasing tissue proteases.[35] There is some evidence in rats that a general tissue protease inhibitor has a beneficial effect during uncomplicated anastomotic healing, yet a detrimental effect after colonic obstruction.[36] The process of creating an anastomosis significantly alters the local microbiota at the site of the anastomosis.[37] There is new evidence that the presence of specific bacterial families and low microbial diversity correlates with anastomotic leakage.[38] Although the details remain to be discovered, the bacterial contribution to healing and to the development of anastomotic complications is likely to be significant.

Microbes: The Common Denominator of Anastomotic Complications?

A role for intestinal microbiota in anastomotic healing has been known for over sixty years. Much of the evidence for this role has been gathered indirectly, in studies where antibiotics are administered and leak rates are examined in both animals and humans. In the aggregate, these studies provide indisputable evidence that microbes are a contributing factor in the occurrence and outcome of leak. In one of the first studies Isadore Cohn performed a colon anastomosis in dogs and devascularized the anastomotic segment until it appeared grossly ischemic. The dogs were then administered either antibiotics or saline directly into the anastomotic site by placing a feeding tube just proximal to the anastomosis. Dogs assigned to antibiotics demonstrated normal healing and reversal of the ischemia, whereas dogs administered saline developed leaks and peritonitis.[39] Since then, numerous animal and clinical studies have shown that oral non-absorbable antibiotics decrease but do not eliminate anastomotic leak rates.[40] These studies provide evidence that microbes play a significant role in anastomotic leak. Yet surgeons do not consistently apply oral, non-absorbable antibiotics as a prophylactic measure to prevent infectious complications.[41] Potentially, the lack of molecular detail and causative inference needed to implicate the role of microbes in these anastomotic leak studies is the reason that surgeons continue to dismiss microbes as important causative agents.

Our lab has been studying anastomotic leak at the molecular level and has provided exciting details that continue to implicate the role of microbes as initiating and causative agents in leak. We have isolated microbial organisms (*Pseudomonas aeruginosa, Enterococcus faecalis*) that, when reintroduced into animals, can cause leak independent of the anastomotic technique itself. The mechanism is a result of the abilities of these bacteria to produce the collagen-degrading enzyme collagenase. Bacteria produce a collagenase that can breakdown intestinal tissues at seven orders of magnitude higher than intestinal tissue

collagenase; these bacterial collagenases are therefore much more likely to alter the dynamics of healing than the host tissue enzymes alone.[42,43] We have also shown that these microbial-derived collagenases trigger intestinal tissues to produce MMP9 (matrix metalloproteinases), which themselves have an important tissue destructive capacity. Surprisingly, both our studies and the studies of other labs have shown that despite the best efforts to deliver intestinal antisepsis prior to surgery (purgatives, oral antibiotics, intravenous antibiotics), these collagenase-producing organisms persist at anastomotic sites.[44]

Since many pathogenic bacteria remain on anastomotic tissues during the healing process, it remains unclear under which circumstances certain bacteria become 'triggered' to cause a leak. Our studies demonstrate that the role of the normal intestinal microbiome is very important in containing the virulence of these pathogens. When the normal intestinal microbiome refaunates after surgery, it can provide colonization resistance against these blooming pathogens. However, if the normal microbiome cannot repopulate itself after surgery, high-collagenase pathogens with the capacity to adhere to and colonize anastomotic tissue may then complicate anastomotic healing. Clinical trials are under development to test this hypothesis in a manner that would inform more effective preventative measures than the current approach of undirected antibiotic elimination of all potential pathogens. It should be kept in mind that the current approach to intestinal antisepsis is based on fifty-year-old culture data that is not only outdated, but, owing to it being culture based, misses many important aspects of the intestinal microbiome such as microbial community structure, phenotype, its proteome and metabolome.[45] New understanding of the role of the intestinal microbiome in health and disease is likely to have a major influence on how we prepare for bowel anastomoses in future patients.

Preparing the Bowel for Anastomotic Surgery: How We Got It Right, Why We Still Have It Wrong

Our understanding of preparation of the bowel prior to surgery has evolved over time. In the first half of the twentieth century, when surgeons recognized that microbes played a role in anastomotic leak and surgical site infection, patients were admitted preoperatively for bowel preparations to decrease the fecal load and eliminate bacteria from the intestinal lumen. Postoperative infection rates decreased from nearly 40% to 20%.[46] Increasingly, the intent was to sterilize the bowel lumen prior to surgery. This was achieved with oral, non-absorbable antibiotics and mechanical cleansing, using large volume osmotic agents, motility agents and enemas. In the 1990s, with the increasing use of intravenous antibiotics at the beginning of surgery and the shift to outpatient bowel preparations, the oral antibiotic component of the bowel preparation and the need for purgative cleansing were considered unnecessary and often omitted.[47,48] The "bowel prep," defined as purgative cleansing agents and oral antibiotics, came under attack and many studies demonstrated that it was not needed to prevent infectious related complications. However, resurgence in bowel prep use has developed due to persistent infectious complications following colorectal procedures. In addition, patient concerns regarding discomfort and the efficacy of the bowel preparation have recently been reevaluated. Observational and randomized clinical trials have

demonstrated that compared to no bowel preparation, mechanical bowel preparation alone provides no benefit in key infectious outcomes.[47] However, when mechanical bowel prep is combined with oral and intravenous antibiotic prophylaxis in colorectal surgery, there is a 44% reduction in surgical site infection.[40]

Throughout the history of intestinal surgery, surgical prophylaxis has been reflective of the understanding of the intestinal microbiome. In the mid-twentieth century, the intention was to eliminate all intestinal bacteria prior to surgery. The integral role that our intestinal microbiome plays in promoting our health and the potential detriments of an imbalanced microbiome were not yet appreciated. Given studies demonstrating improvement in surgical site infection after colorectal surgery—with the use of oral and intravenous antibiotics and mechanical bowel preparation—it is becoming increasingly clear that intestinal bacteria play an important role in infectious complications. We know that mechanical bowel preparation and antibiotic use dramatically alter the intestinal microbiome.[49,50] Yet how to specifically eliminate the 'bad actors' in our microbiome while at the same time preserving our health-promoting microbiota remains a challenge. Surgical prophylaxis has had to evolve with the growing understanding of the anatomic variation of the intestinal microbiome; surgery on the jejunum requires different preparation and prophylaxis from surgery on the sigmoid colon. Increasingly, surgical practice reflects the biologic composition of the various intestinal bacterial ecosystems: no bowel preparation or oral antibiotics for the lower-microbial-load environment of the small bowel, but mechanical bowel preparation and oral antibiotics for the high-microbial-load environments of left-sided colon and rectum.[41] The existing body of evidence upon which we are basing our practices is unfortunately weak. There is now an opportunity to understand more completely the impact of present practices and to refine approaches using genetic analysis of the intestinal microbiome at specific regional and spatial niches (i.e., anastomotic tissue sites). Such studies will help to elucidate the complex biological processes present on and within anastomotic tissues. This will in turn inform the path forward to a more pathophysiologically based intestinal antisepsis method of containing the harmfulness of certain microbes while preserving the health benefits of others.

Conclusion: How Do We Move Forward in the Prevention of Anastomotic Healing Complications?

The creation of an anastomosis requires meticulous attention to detail, both technically and biologically. Anastomotic healing complications are not as simple as too much or not enough collagen; not as simple as patient risk factors; and not as simple as bad bacterial actors. Development of an anastomotic stricture or leak is a result of the complex interactions of genetics, the microbiome, operative technique, a patient's antecedent health, prior patient exposures, the subsequent hospital course, and exposures ranging from infectious agents to antibiotics. Further research evaluating the relationship and impact these many factors have on the progression of anastomotic healing is needed. In order to develop a higher-resolution pathophysiologic understanding, we need methods to directly and serially examine anastomoses and extract meaningful information. With further understanding of the dynamic factors that impact healing at the anastomotic site, we will be able to develop more

informed and scientifically based interventions and preventive measures. Technological advances are now available to execute these studies in real time and to develop a more complete understanding of the impact of the intestinal ecosystem on anastomotic healing.

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Key Points

1. Anastomotic leak and anastomotic stricture remain persistent and poorly understood phenomena in gastrointestinal surgery.
2. Inconsistent definitions and reporting of anastomotic complications lead to difficulty in comparing the results obtained in different studies and the impact of interventions.
3. Few interventions have led to a statistically significant decrease in the incidence of anastomotic complications.
4. Consistent definitions and improved understanding of the pathophysiology of anastomotic healing complications will lead to interventions that target underlying causes of the complications themselves.

Table 1

Proposed Classification for Postoperative Anastomotic Disruption

	Imaging Finding
Class 1	Free pelvic or presacral fluid on CT with no extravasation of contrast medium
Class 2A	Postoperative *perianastomotic abscess* with no extravasation of contrast medium
Class 2B	Postoperative *remote intra-abdominal abscess* with no extravasation of contrast medium
Class 3	Presacral extravasation of contrast medium
Class 4	Free extravasation of contrast medium

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