

# Healing in Gastrointestinal Anastomosis

Rapid and effective wound-healing is of paramount importance to the surgeon and to the patient. Failure of wound-healing generally leads to potentially life-threatening complications, additional surgical procedures, increased length of hospital stay, increased cost, and long-term disability. Although gastrointestinal healing is a topic rarely reviewed in surgical literature, it is an essential aspect of any procedure involving the gastrointestinal tract. Despite many recent advances in surgical technologies, patients continue to suffer from anastomotic disruptions and strictures. This translates into an astronomical financial burden on society, and an even greater intangible cost to the patient in terms of disability, discomfort, and diminished quality of life.

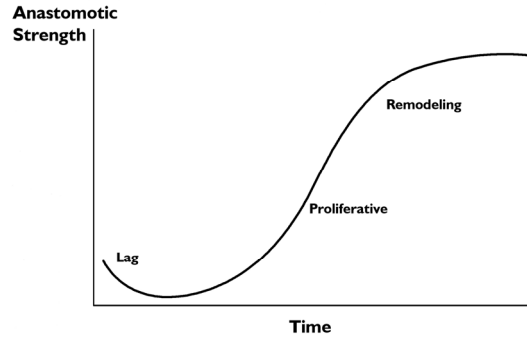
In the coming chapters, we will review the biological response to injured tissue and discuss local and systematic factors that influence gastrointestinal healing. We will compare methods of measuring the collagen content and strength of the newly formed gastrointestinal anastomosis.

## Biologic Response to Tissue Injury

A wound is a disruption to normal structure and function of tissue after a noxious insult. Wound healing is a series of carefully regulated steps designed firstly to reestablish an immune barrier, and secondly, to repair injured tissue. Initiation of the pathway begins immediately after a wound occurs, and follows a predictable, orderly reparative timetable.

The classic phases of wound healing are described below.

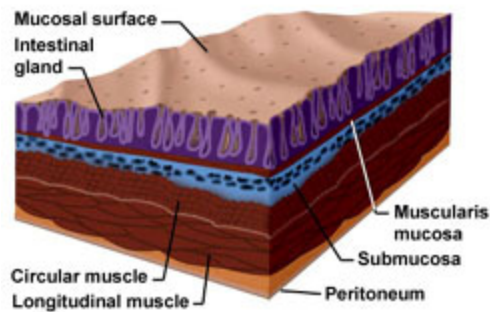
1. ***Inflammation or “lag” phase:*** Platelets first create hemostasis at the site of injury by forming an insoluble fibrin-based clot. Increased permeability of vessels adjacent to the injury facilitates the efflux of inflammatory cells into the wound. **Neutrophils** are initially the dominant cell type, and their role is to rid the wound of invading microbes. Within 2-3 days, **monocytes** and tissue **macrophages** predominates. Macrophages synthesize and release a multitude of tissue growth-factors that are absolutely critical to the normal progression of tissue repair.
2. ***Proliferation:*** The proliferative phase begins with the arrival of fibroblasts at the wound site. Fibroblasts become the major cell type by day 4, and their arrival is regulated by various growth factors. Fibroblasts replace the provisional matrix (established through the inflammation phase) with collagen-rich granulation tissue. Normal soft tissue contains 80% type I collagen and 20% type II collagen. In contrast, acute wound granulation tissue contains approximately 30-40% type III collagen. Collagen synthesis requires hydroxylation (6) of lysine (7) and proline (8) residues. Cofactors necessary for hydroxylation include ferrous iron, molecular oxygen, molecular oxygen and vitamin c. Angiogenesis occurs at this time to allow good oxygenation, and to supply essential nutrient building blocks to the healing wound.
3. ***Remodeling:*** with time, newly formed granulation tissue undergoes remodeling, and the density of macrophages and fibroblasts is reduced. Thin collagen fibers transform into thick bundles, and the percentage of type III collagen is reduced to 20%. Wound contraction occurs as fibroblasts pack thick collagen bundles into contractile units.



## Healing in the Gastrointestinal Tract

### *Anatomy*

The gastrointestinal tract (GI) consists of four layers (with exception of the esophagus and the low rectum): mucosa, submucosa, muscularis propria and serosa. The mucosal layer consists of epithelium (generally columnar cells), lamina propria (loose connective tissue containing collagen), and muscularis mucosa (a thin layer of smooth muscle cells). Mucosal disruptions are repaired by migration and hyperplasia of epithelial cells. This seals the defect, and creates a barrier to luminal bacteria. Direct apposition of mucosa allows repair in a few days.



In 1887, Halsted discovered that the submucosa provides the GI tract with the majority of its tensile strength. The bulk of collagen is contained within this layer, along with blood vessels, lymphatics, and nerve fibers. Type I collagen predominates (68%), followed by type III collagen (20%) and type V collagen (12%). The muscularis propria consists of smooth muscle cells intermixed with network of collagen. The collagen content in this layer increases significantly in response to chronic obstruction.

The serosa is a thin layer of connective tissue that covers the muscularis propria. When creating anastomosis, direct apposition of this layer minimizes the risk of leak.

## Physiology of Anastomotic Healing

As described above, healing in gastrointestinal anastomosis begins with inflammation or the “lag phase”. An initial hemostatic response with vasoconstriction is followed by increased vessel permeability. This facilitates the efflux of inflammatory cells (Neutrophils) into the wound. Shortly after, macrophages can be seen at the anastomotic site, where they synthesize and release tissue growth factors. Granulation tissue in the anastomosis marks the beginning of the proliferative phase, and wound collagen undergoes both lysis and synthesis. The strength of the anastomosis is mainly derived from collagen fibrils, located within the submucosal layer. During the first postoperative days, anastomotic strength is limited as collagen is degraded secondary to collagenase activity at the site of the injury. Early anastomotic strength is therefore dependent on the suture- or staple-holding capacity of existing collagen, until a large amount of new collagen can be synthesized by both fibroblasts and smooth muscle cells. Post operatively, anastomosis will be weak for 1 or 2 days until this occurs. The final phase of healing involves maturation of the newly formed anastomosis. The density of macrophages and fibroblasts in the anastomosis decreases, and newly formed collagen is transformed into thick bundles and contractile units.

## Differences between Skin and GI Healing

Although the three classic phases of wound-healing were originally studied on skin, they exist in all tissues, including the GI tract. There are some significant differences between skin and GI healing.

The GI tract consists of three subtypes of collagen, in contrast with skin, which consists of only two subtypes. In skin, collagen is produced solely by fibroblasts, while in the GI, smooth muscle cells produce collagen as well. Smooth muscle cells are located in both the muscularis mucosal layer and the muscularis propria of the GI tract.

The environment for wound healing is substantially different in an anastomosis due to the presence of shear stress (secondary to intraluminal bulk transit and peristalsis), as well as aerobic and anaerobic bacteria. Extremely important is the downregulation of vascular perfusion to the GI track in a state of hypovolemic shock. Anastomotic failure can be directly attributed to ischemia (15) in the anastomotic area.

Although a more rapid gain in strength occurs in the GI tract than in cutaneous wound, neither regain their full preoperative strength. Martens and Hendriks found that collagen synthesis occurs more quickly and to a greater extent in a wounded ileum vs. a wounded colon in the rat model. Other studies found the decrease in anastomotic collagen (secondary to collagenase activity) less pronounced in the ileum. Small bowel anastomoses approach the strength of unwounded tissue within four weeks following an injury, while colonic anastomoses approach 75% of normal strength after four months.

## Failure of Gastrointestinal Healing

As described, wound-healing is a complex process that involves the interaction of predictable, orderly, and time-dependent components. The outcomes of healing can be measured over time using wound healing trajectory. The classic acute wound healing trajectory is a sigmoid shaped (as shown

in figure 1). The curve begins with a flat “lag phase”. The risk of wound failure is greatest at this time, especially in GI healing, when collagenase activity is greatest. After 48 h, the strength in esophageal anastomoses decreases by almost 40%, while colonic anastomoses lose 70% of their initial strength. Proliferation is demonstrated on the graph with a steep slope.

Wound healing failure occurs when there is an abnormality in either the degree or the duration of one of the components of tissue repair. Local and systemic factors may cause failure of GI healing

## Tissue Perfusion

Ischemic tissue does not heal well. Wound-tissue oxygenation depends on three factors: vascular anatomy, vasomotor (16) control, and arterial tissue oxygen pressure. The surgeon, therefore, needs to ensure that the patient has good local perfusion to the healing anastomosis, adequate cardiac output, and optimal oxygen saturation levels.

Local tissue perfusion depends on preservation of vascular arcades, and avoidance of anastomotic tension. Tension is least tolerated in the colon. It is important to avoid hypovolemia in the preoperative period, as perfusion to the GI tract will be decreased in order to support critical organs.

Finally, adequate oxygen delivery is necessary for collagen synthesis. Mature collagen formation fails when tissue oxygen pressure drops below 40mm hg. Below 10mm hg, growth factors, angiogenesis, and epithelization are all impaired, leading to anastomotic failure.

## Other Factors that Contribute to GI Tract Healing

Wound healing requires energy and adequate nutritional intake by the patient. Malnourished patients are predisposed to wound healing failure as they lack of the necessary vitamins and minerals for repair. These includes vitamins A,C, and B6, all required for collagen synthesis and cross-linking, as well as zinc and copper. Zinc and iron acts as cofactors to many reactions involved in DNA synthesis, protein synthesis, and cellular proliferation. Zinc or copper deficiencies result in fewer fibroblasts, and impacts collagen synthesis.

Local infection impairs wound healing by prolonging the inflammatory phase, and inducing the increased expression of tissue proteases.

Elevated tissue proteases digest growth factors, and thus delay epithelization and collagen deposition. Localized preoperative or perioperative bowel irradiation was not shown to compromise anastomotic healing in animal model. It is hypothesized that if radiation is given prior to the influx of macrophages into the wound, a normal healing cascade will occur.

## Ischemia and Anastomotic Healing

The effect of ischemia on anastomotic failure is well documented. The anastomoses leak due to inherently tenuous blood supply. Perfusion of the conduit and anastomosis often depends on a single vascular pedicle delivering only a small fraction of the original blood supply. The most distal aspect of the conduit is at risk for diminished perfusion and diminished anastomotic healing. A

retrospective review by Briel showed that among 393 patients who underwent esophagectomy, conduit ischemia occurred in 36 (9.2%), with a mortality of 13.9%. Conduit ischemia was recognized as the major factor for leak rate.

Disruption of microcirculatory blood flow at the level of the anastomosis is one of the major factors leading to anastomotic failure. Decreased tissue perfusion begins intraoperatively, and can lead to necrosis and tissue breakdown in the early postoperative period. Studies showed that the anastomosis was at highest risk during the first 24h, and that microvascular recovery has improved anastomotic perfusion by 96h.

Anastomotic ischemia is difficult to detect clinically. Intraoperatively, it is common practice for surgeons to assess the perfusion of the tissue according to whether of the mucosa bleed, and whether there are color changes. Dopler ultrasound is also used in adjacent mesentery to assess blood flow. One study, which compared blood flow to the gastric fundus intra and postoperatively in 44 patients, found a significantly lower postoperative blood flow volume in those patients with leakage vs. those without.

## Summary

- Wound healing includes three phases: inflammation, proliferation and remodeling.
- Any interruption with each phase or its duration will result in failure of wound healing and can result in the breakdown of the anastomosis
- Anastomosis is weakest on days 3-4, regarding collagen breakdown in the inflammation phase.
- In the inflammation phase and the proliferation phase, anastomosis depends on suture materials to hold it.
- After approximately seven days, the anastomosis can hold independently.
- Foreign materials in this phase are not needed and might increase inflammation and scarring.

Compression anastomosis can reduce the time required for the anastomosis and the results of inflammation to heal.