Review Article (Current Status of Colorectal Cancer Surgery)

Management of anastomotic leakage after rectal surgery: a review article

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Abstract: Anastomotic leaks (ALs) are associated with increased perioperative morbidity and mortality, prolonged length of stay, higher readmission rates, the potential need for further operative interventions, and unintended permanent stomas; resulting in increased hospital costs and resource use, and decreased quality of life. This review article is to present definition, diagnosis and management strategies for AL after rectal surgery.

Keywords: Anastomotic leak (AL); rectal surgery; leaks; management

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Introduction

Colorectal surgery is associated with significant morbidity and mortality. Anastomotic leak (AL) is the most common cause of death after colorectal surgery (1,2). ALs are associated with increased perioperative morbidity and mortality, prolonged length of stay, higher readmission rates, the potential need for further operative interventions, and unintended permanent stomas; resulting in increased hospital costs and resource use, and decreased quality of life (3-8).

The development of an AL is also associated with higher local recurrence rate and worse disease-free survival (9-12).

Definition of AL

There has been no universally accepted definition of AL at any site along the gastrointestinal tract. In a review of 97 studies, for example, 56 different definitions of an AL were found (13).

In 2010, the International Study Group of Rectal Cancer proposed a uniform definition of AL as a defect at the anastomotic site leading to a communication between the intraluminal and extraluminal compartments (14). Based on above definition, in 2015, International Multispecialty Anastomotic Leak Global Improvement Exchange (IMAGInE) defined AL of entire gastrointestinal tract, as a defect of the integrity in a surgical join between two hollow viscera with communication between the intraluminal and extraluminal compartments (15). According to severity and clinical presentation, the grading system allows AL to be classified into one of three grades (A, B, or C). Grade A leaks are those managed without an invasive intervention, grade B leaks are those managed with invasive intervention other than repeat surgical intervention (e.g., percutaneous drainage), and grade C leaks are those requiring repeat surgical intervention and often diversion.

Incidence

The reported incidence varies from 6% to 30% (1-3,16-18), largely based on the criteria for diagnosis and the length of follow-up, with an average of 11% (3). The higher rate is seen in lower anastomoses (1-3,16-18). Lower overall incidence of AL is noted when performed by experienced surgeons (19). While the highest rate, 10% to 20%, was seen in coloanal anastomosis (20,21).

Risk factors

The location of the anastomosis is one of the most important risk factors for AL (1-3,16-18,20,21), especially with an anastomosis within 6 cm from anal verge (22). In addition, male gender, steroid use, pre-operative chemoradiation, hypotension, diabetes, smoking, and obesity are known risk factors (23-27). Malnutrition has also been reported to be associated with increased AL rate (28).

Additionally, data continue to emerge citing the local microbiome as a critical factor in the development of an AL (29). Matrix metalloproteinases (MMPs) and collagenases are part of the body's normal response to injury. However, these proteins have been implicated as important mediators of AL (30). Animal studies have suggested that certain bacterial strains that produce these collagenolytic proteins (*Enterococcus*, *Pseudomonas*, or *Serratia* species) may contribute to the development of AL (30-32).

Diagnosis and clinical presentation

Anastomotic has been reported to increase the mortality rate from 1.6% to 12% (33). However, early diagnosis of AL can be difficult owing to poor specificity of the most common signs and symptoms.

Classic presentations of AL are severe abdominal pain, diffuse muscle guarding with positive peritoneal signs, and hemodynamic instability; in this setting, the diagnosis is straightforward. However, AL often presents with a diverse array of cardiovascular, pulmonary, and gastrointestinal symptoms that are also seen in patients without any AL. Besides, the positive predictive value of abnormal vital signs after bowel resection is only 4% to 11% (34). Drains placed intraoperatively may provide early clues to a leak if fecal material is seen to exit, but drains are not always reliable (35,36).

In general, AL is diagnosed within the first 2 weeks after surgery (37-39). The majority of ALs are diagnosed between the 7th and 12th postoperative days, while up to 42% of patients are diagnosed after the patient has been discharged, and up to 12% occur even beyond postoperative day 30 (37,40). Early AL is defined as AL is diagnosed within postoperative day 6 and late AL as after postoperative day 6 (27,41).

Early and late ALs have different pathophysiology. For early AL, technical failure of the anastomosis resulting in immediate anastomotic dehiscence is the reason. The quality of the surgery seems have more influence in early AL than in later AL. For late AL, the frailty of patients and tissues, which may suggest poor healing process at the anastomotic site is the factor (27).

Late leaks often present insidiously with low-grade fever, prolonged ileus, and nonspecific symptoms attributable to other postoperative infectious complications. Small, contained leaks present later in the clinical course and may be difficult to distinguish from postoperative abscesses by radiologic imaging, which making the diagnosis uncertain and underreported. There is a need for more sensitive, specific and predictive diagnostic markers that will enable diagnosis and intervention.

Biochemical markers

C-reactive protein (CRP) is an inflammatory-induced marker with peak levels observed about 48 hours after stimulation. CRP has been the most extensively studied biomarker, shown to have a negative predictive value of 89–97% for AL (42). CRP values below specific cutoffs between postoperative days 3 and 5 are negative predictive of ALs (42,43). Cutoff levels of CRP varied (range, 100 to 172 mg/L) between studies or between postoperative days. Otherwise, overall positive predictive value of AL is low (between 21% and 23%). Thus, higher levels of postoperative CRP require further investigation to confirm any presence of a leak (42,43).

Procalcitonin (PCT) is the prohormone of calcitonin with physiologic serum concentrations below 0.5 ng/mL; produced in C cells of the thyroid and is a more specific marker of bacterial infection than CRP. PCT level above threshold of 2.0 ng/mL has been highly suggestive of sepsis (44). PCT has a shorter induction period (4 to 12 hours) than CRP, and microbial infection stimulates the release of PCT from a wide variety of tissues for a sustained half-life of 22 to 35 hours. A recent meta-analysis demonstrated that low PCT levels on POD 3 and 5 had high negative predictive values, similar to CRP, and reliably excluded AL (45). The serial values instead of isolated levels offers more potential in the diagnosis of ALs.

The result of PCT combined with CRP in early diagnosis of AL keeps controversial (45,46).

The level of CRP, lipopolysaccharide-binding protein (LBP), and PCT in drain fluid can also serve as screening tools in detecting AL (47).

den Dulk *et al.* developed the Dutch leakage (DULK) score, using easily accessible clinical parameters scorable on a daily basis, such vital signs, urinary output, mental status, physical examination, laboratory data and nutrition status, to predict early AL (48,49).

Imaging

Computed tomography (CT) has taken place of water-soluble contrast enemas, as the most employed test when diagnosing AL (50). While the specificity of CT is quite high (>84%), the sensitivity is only 68–71% (51,52). CT with retrograde contrast enema (RCE) is accurate for diagnosing postoperative colorectal AL. Contrast extravasation is the most reliable sign while it is not always present (as low as 15% to 17%). RCE should be considered during CT for suspected AL (52). Perianastomotic air/fluid levels appear to be the most reliable finding other than extravasation of contrast (52-54). In addition, fluid and inflammatory stranding are nearly always present in an early postoperative CT scan. For this reason, AL is difficult to diagnose on CT in the first 3 or 4 days postoperatively (55).

Management

Management depends on the clinical presentation and the severity of symptoms. Early resuscitation to avoid septic shock is the key to avoiding multisystem organ failure and even death following AL. Highly suspicion, early recognition with an aggressive approach and intervention, prior to development of contamination and subsequent sepsis, are important.

Antibiotics

ALs require broad-spectrum antimicrobials due to the increasing rates of multidrug-resistant organisms, including enterococci, *Pseudomonas*, and extended-spectrum β-lactamase-producing *Enterobacteriaceae* (*ESBL-E*) (56). Superior outcomes were achieved with combination therapy (≥2 different classes of antibiotics) than monotherapy (57). Antifungal agents should be considered in patients with severe sepsis or septic shock and a postoperative intraabdominal infection (57,58). In general, abscesses less than 3 cm in size can be managed with antibiotics alone when the patient is clinically stable (59,60).

Drain

For abscesses greater than 3 cm in size, percutaneous drainage is a viable option with success rates up to 85% (61).

Some advocate placing a transanal drain, such as a small Malecot catheter, through the anastomotic defect. Follow-up radiographic surveillance of the abscess cavity by the instillation of contrast through the drain. The drain remains in place until the abscess cavity closes to the size of the drain. Successful resolution of the defect does not remove the risk of long-term complications associated with ALs such as stricture formation and poor bowel function (62,63).

Source control

Source control is defined as any intervention that is used to remove the focus of infection, prevent further contamination, and restore anatomic and physiologic function. Inadequate source control has a negative impact on patient survival following an AL. Failure to achieve source control is more likely to occur in patients with advanced age (>70 years), multiple comorbidities, higher severity of illness (APACHE II ≤15), and a greater degree of peritoneal involvement. Early source control improves mortality by minimizing the duration of severe sepsis or septic shock and preventing the progression to multiple organ failure (64). Based upon current guidelines, it is recommended that an intervention to obtain source control should be initiated within the first 12 hours after the diagnosis of severe sepsis or septic shock when possible (58). Patients with generalized peritonitis and/or signs of severe sepsis or septic shock typically require laparotomy with washout, débridement, and drainage to obtain source control. There are 2 surgical treatment strategies following an initial emergency laparotomy planned relaparotomy and relaparotomy only when the patient's condition demands it ("on-demand"). Patients in the on-demand relaparotomy group had shorter median intensive care unit stays, shorter median hospital stays, reduction in relaparotomies, and reduced direct medical costs per patient (65,66).

Anastomotic salvage versus takedown

Management of ALs has been predominantly based on the surgeon's own personal experience because little evidence exists to help guide management.

Takedown of the anastomosis with creation of an end-ostomy is the most frequently applied approach. This strategy, however, is associated with excessive numbers of patients with permanent fecal diversion. and reduced quality of life because of ostomy-associated complications such as leakage, dermatitis, peristomal hernia, and sexual dysfunction. Another viable option includes salvage of the large bowel continuity using a loop-ostomy either alone or in combination with anastomotic repair or redo of the anastomosis. Takedown of the anastomosis results in a 2.5-fold increase in the rate of permanent fecal diversion when compared with anastomotic salvage using either a loop ostomy alone or in conjunction with repair or revision of the anastomosis (67,68).

More evidence supports the use of anastomotic salvage and loop diversion in patients with an extraperitoneal anastomosis (i.e., a low pelvic anastomosis). Reoperations for AL typically take place in a hostile abdomen in the setting of a severe inflammatory response and are usually surrounded by the dense adhesions of the early postoperative period. In addition, the inflammatory reaction around the AL commonly precludes safe surgical dissection. In these situations, the anastomosis should be left in place with drains placed in close proximity and a proximal diverting ostomy created. Anastomotic salvage with loop diversion resulted in statistically fewer postoperative deaths, recurrent sepsis, reoperations, and permanent stomas than anastomotic takedown (67-71). Anastomotic repair without proximal diversion is not recommended because increasing mortality rate in low rectal anastomoses.

Nonoperative interventions

Patients who have lower severity leakages, and/or previously diverted are more likely to successfully undergo nonoperative management. It should be noted that a protective stoma may reduce the incidence of clinical leakage but is not significantly associated with decreased mortality rates when patients have ALs (72,73).

A successful interventional drainage significantly lowers mortality rate, comparing with medical treatment alone (74). Percutaneous drainage, is an effective therapy in patients with ALs who are hemodynamically stable and do not have signs of diffuse peritonitis, resulting in lower hospital costs and shorter hospital stays compared with surgical management. Overall success rate after 1 or 2 drainages was 78% and residual collection after a first drainage is an independent predictor of unfavorable outcome (75).

Even with adequate source control and fecal diversion, many low pelvic leaks do not heal, leaving a chronic sinus tract and resulting in a permanent stoma in more than half (56%) of patients (6). AL after restorative resection for rectal cancer leads to early adverse consequences on bowel function and quality of life even (owing to chronic inflammation and fibrosis, resulting in loss of reservoir capacity) when anastomotic continuity can be maintained (76).

Many surgeons rely on a wait-and-see approach and follow the anastomosis expectantly. One potential drawback of this practice is that definitive treatment of the leak will be delayed if the leak does not close by itself. Emerging therapies, focusing on promotion of closure of the leak are reported.

Stent

Stent migration is the major issue. The colorectal anastomosis must be an end-to-end anastomosis, and the distal end of the stent must be at least 5 cm above the anal verge. Therefore, stents are not effective for low anastomoses. The current covered stents do not have a large enough diameter to minimize stent migration. Some have described the use of endoclips to secure the stent in place, but that has not proven particularly effective. In the largest series to date, fully covered colonic stents were used in the treatment of 19 of 22 patients with colorectal ALs, while uncovered colonic stents were placed in the remaining three patients. Complete closure of the leak occurred in 19 of the 22 patients (86%), allowing for closure of the ostomy in all patients. In 15 patients, leaks were closed after an average time of 3 months; four additional patients required a second stent. All 19 patients initially experienced incontinence that eventually resolved after an average of 14 weeks (77-79).

Endoscopic transanal vacuum-assisted rectal drainage

As first described by Weidenhagen in 2008, endoscopic vacuum (E-Vac) therapy has showed to be an effective method in closing defect by granulation tissue formation and wound contraction (80). E-Vac therapy for cavities associated with ALs involving the rectum has resulted in impressive closure rates (85.7%) and low permanent stoma rates (18.9%). The highest closure rates and lowest permanent stoma rates were seen in patients with proximal diverting stomas and/or early treatment (<6 weeks postoperatively). Unfortunately, the use of E-Vac is very time and resource intensive, requiring considerable patience and tenacity both on the part of the surgical endoscopist and the patient; patients should be counseled and informed of the expected number of endoscopic changes (7 to 11) and treatment duration (18 to 34 days) required for leak closure (80,81) .

The sponge is exchanged every 48–72 hours and is downsized as the cavity decreases in size. Treatment is stopped when the cavity is less than 1 cm in size. It seems to be more effective if placed early when the rectum is more pliable prior to the development of associated fibrosis. It has been used in very distal anastomoses and in the setting of proximal diversion.

Endoscopic clip application as a method to re-approximate the anastomotic dehiscence has also been described (82,83). Although the data are limited to small case series, this technique seems better for small leaks less than 1.5 cm in size in the absence of a pelvic collection. It has also been used in conjunction with the transanal sponge technique once that cavity is small enough.

Surgery

The operative management of AL can be very challenging due to gross contamination, and severe inflammation. Traditional management of an AL included either exteriorization of the leaking anastomosis or resection of the anastomosis with the creation of an end stoma and Hartmann pouch or mucus fistula (38). While certainly effective at controlling the leak, dissection around the anastomosis can prove difficult with the risk of injury to surrounding structures. In addition, restoration of intestinal continuity under these circumstances requires a subsequent major operation to reverse, and as a result, many end stomas are never reversed (70).

While resection of the anastomosis may seem desirable, it is not always feasible and, under certain circumstances, may be deleterious. Under these circumstances, a more desirable option may be drainage (either operatively or percutaneously) and proximal diversion (84).

Patients who do not improve with nonoperative measures or who have sepsis and peritonitis must undergo surgical treatment. Source control with washout and fecal diversion are the main goals of surgical intervention for AL. Fecal diversion can be accomplished by taking down the anastomosis and creating an end colostomy, proximal diversion with a loop ileostomy while leaving the leaking anastomosis alone, or repair or revision of the leaking anastomosis with proximal diversion (68).

Minimally invasive techniques

The role of minimally invasive surgery in the treatment of colorectal ALs is an active area of study. We published our own experience of combined laparoscopic and transanal (hybrid) approach to treat postoperative colorectal ALs. It is feasible and safe in the management of early postoperative colorectal ALs in selected patients. It could possibly reduce early and late postoperative morbidity associated with ALs or their repair (85).

Conclusions

AL is defined as a defect of the integrity in a surgical join between two hollow viscera with communication between the intraluminal and extraluminal compartments. According to its severity and clinical presentation, it can subgroup to three grades (A, B, or C). Risk factors for AL are the anastomosis within 6 cm from anal verge, male gender, steroid use, pre-operative chemoradiation, intraoperative hypotension, diabetes, smoking, and obesity. Malnutrition may have some role also in AL.

Early AL implies technical failure of the anastomosis resulting in immediate anastomotic dehiscence, while the frailty of patients and tissues with poor healing process may contribute to late AL.

Early detection of leak is important but could be difficult. Highly suspicion and aggressive use of imaging and biomarkers of inflammation may play roles in detection.

Management depends on the clinical presentation and the severity of symptoms. Early resuscitation, source control, nonoperative interventions, and surgery (either by laparotomy and minimally invasive method) are all essential in management of ALs.

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Footnote

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