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REVIEW ARTICLE

Anastomotic Failure in Colorectal Surgery: Where Are We at?

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Abstract
Anastomotic leak (AL) can be a devastating complication in colorectal surgery. While it is less frequent in the modern era, it still results in significant morbidity and mortality, prolonged hospital stays and increases the costs and demands on health services. There is inevitable interplay between patient physiology and technical factors that predispose a patient to AL. Obesity, preoperative total proteins, male gender, ongoing anticoagulant treatment, intraoperative complication and number of hospital beds have been identified as independent risk factors. This has led to an online risk calculator for AL. Non-steroidal anti-inflammatory drugs and neoadjuvant chemoradiotherapy have also been implicated, but no significant evidence has yet been found to support causation. In addition, technical factors such as type of anastomosis, mechanical bowel preparation, drains, omentoplasty and faecal diversion have failed to show significant differences in AL rates. Early diagnosis and intervention in AL is essential in reducing the rates of morbidity and mortality. Clinical assessment has high sensitivity but low specificity and should be used in combination with imaging techniques to get a diagnosis. C-reactive protein is also a useful marker. The management will depend on the grade of AL and the clinical state of the patient. Management options include conservative measures such as antibiotics and/or percutaneous drainage to more invasion procedures such as open drainage and/or Hartmann's procedure. In conclusion, ALs will forever pose challenges to the surgeon in diagnosis and management. It is often the yardstick by which each surgeon is measured and is the source of significant morbidity to patients and health care services worldwide. As a result, a low threshold for investigation and intervention is mandatory to ensure better outcomes and lower overall mortality and morbidity.

Keywords Anastomotic dehiscence · Anastomotic leak · Anastomotic failure · Colorectal surgery

Introduction

Anastomotic leak (AL) can be a devastating complication in colorectal surgery. Albucasis was the first to describe an intestinal anastomosis in his book *Al Tasrif* (circa 1000 CE) using Arabian Ant stitches and treated animal gut. Over time, surgical technique has evolved to improve safety and outcomes after bowel anastomoses, with Travers, in 1812 [1], who described an everting stitch to anastomose bowel ends. Following this, Lembert stressed the importance of serosal apposition and inverting sutures [2] in the healing of anastomoses. Shortly after this, the first mechanical anastomotic device, the Murphy Button, was described in 1892 [3]. Despite the advances of the nineteenth century, the absence of aseptic technique and anaesthesia meant the success rates in this period was poor, with reports of 26.3% mortality, and 35.8% of those "cured" were left with an enteric fistula [4].

In the modern era, anastomotic failure, while less frequent, still results in significant morbidity and mortality, prolonged hospital stays and increases the costs and demands on health services. The aim of this clinical review is to summarise the current evidence, highlighting factors which contribute to anastomotic leak (AL) and how to diagnose and manage it when it occurs.

Definition

The definition of AL used in case series varies in the literature and even amongst surgeons. A meta-analysis found that only 29 of 47 studies reporting on anastomotic leaks included a

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definition, which varied from the presence of an abscess, or feculent drainage and discharge, to signs of peritonitis and to contrast extravasation [5].

A survey of surgeons regarding their definitions of leak showed that 94.2% of surgeons agreed that contrast extravasation constituted an AL, and 91.8% that faecal material in wounds or drains constituted a leak irrespective of surgical management. However, disparity existed in patients with a radiologic collection requiring antibiotics or percutaneous drainage, with 46.6 and 51.4% of respondents respectively, classifying these findings as AL, increasing to 69.2% if surgical intervention is required [6].

The International Study Group of Rectal Cancer proposed a definition of AL specifically regarding anterior resections as being "a communication between the intra and extraluminal compartments owing to a defect in the integrity of the intestinal wall at the anastomosis between the colon and rectum or colon and anus" [7].

Epidemiology

The rates of AL reported in the literature vary depending on the site of anastomosis, with ileocolic anastomoses between 0.5 and 6%, colocolonic anastomoses between 0 and 9% and colorectal anastomoses between 0 and 20% [8–13].

Leak rates with rectal anastomoses have been shown to directly relate to height above the anal verge, with reported leak rates of 1.7%, and 4.1 and 7.3% for high, low and ultra-low anterior resections respectively [9, 14].

Aetiology

There is inevitable interplay between patient physiology and technical factors that predispose a patient to AL. The evidence regarding each will be discussed in turn.

Patient Factors

Age

Interestingly, patient age is not a statistically significant factor in AL. This finding has been borne out of several large series [14–16]. Nevertheless, increasing patient age does correlate with increased mortality related to AL with a reported mortality of 5.2, 18.3 and 30.1% in < 65-, 65–80- and > 80-year-old patients respectively [16].

Gender

Multivariate analyses performed by several large series support higher AL rates in male patients in the order of 1.38 to 3.5 times more likely to have a leak than women [14–17]. It is postulated that the narrower pelvises with increase in technical difficulty are contributing factors.

Obesity

Obese patients with BMI > 30 have higher rates of AL in some series, with odds ratios (OR) between 2.2 and 3.78 compared with non-obese counterparts [17, 18]. However, this finding is not supported in other large series on both univariate and multivariate analyses until this year. In addition, the French study found that BMI was significant only in those undergoing low rectal anastomoses.

Nutrition

There is a paucity of data in relation to nutritional assessment as a risk for anastomotic leak. This is hampered by the lack of a reliable marker for what is intuitively important in healing, with albumin being a poor surrogate. One study reported a statistically significant result with an OR for AL in the order of 6.65 and 24.75 in moderate hypoalbuminaemia (2.5–3.5 g/dL) and severe hypoalbuminaemia (<2.5 g/dL) respectively [19]. This is supported by another group looking at 343 patients with Crohn's disease who found a preoperative albumin of < 30 g/dL was significantly associated with the development of AL [20].

Preoperative weight loss > 10% has been identified as a predictor for anastomotic complications after ileocolic resection for Crohn's disease [21] with an odds ratio of 6.23 (1.75–22.5).

A recent prospective Spanish study with 3193 patients investigating AL after colon resection for cancer found obesity, preoperative total proteins, male gender, ongoing anticoagulant treatment, intraoperative complication and number of hospital beds to be independent risk factors after multivariate analysis [22]. The results of this study have led to the development of an AL risk calculator using a modification of the nomogram published in the paper [23]. It aims to aid preoperative patient counselling and surgeon decision-making, with the aim of providing individualised patient care. This calculator is yet to be validated and can be found at http://anastomoticleak.com

American Society for Anesthesiologists Score

A large series looking at data from the Dutch Surgical Colorectal Audit of 15,667 patients reported higher AL rates in American Society for Anesthesiologists (ASA) III and IV patients compared with ASA I and II (9.2 vs 7.1% $p < 0.001$) [16].

Inflammatory Bowel Disease/Immune Suppression

Crohn's disease patients have an OR of 3.31 compared with patients without inflammatory bowel disease, in developing AL [15]. Crohn's patients on steroids (defined as preoperative

steroid use > 3 months duration) have an OR of 5.95 (1.04–34.1) in developing septic complications after anastomosis in one study [20]. In a cohort of patients receiving steroids for pulmonary disease, there was a significant association between steroid use pre- and perioperatively and AL [24]. Conversely, immunomodulator use such as azathioprine has not been found to be associated with an increase in anastomotic complications [25].

A recent systematic review of Crohn's disease patients undergoing surgery while on an anti-TNF agent has suggested a modest increase in abdominal septic complications, OR of 1.47 (1.08–1.99) [26].

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are often included in postoperative enhanced recovery protocols, as an opioid-sparing agent. A recent systematic review on NSAID use suggests a concerning association with AL with the use of non-selective anti-inflammatory agents with a pooled adjusted OR 3.86 (1.18–12.67; $p = 0.030$). This association was not seen with selective COX-2 inhibitors [27]. This review described significant heterogeneity and confounding factors by way of selection bias, inadequate control for location of tumour and type of surgery and open and laparoscopic as well as enhanced recovery protocol uptake (five RCTs and three retrospective cohorts). Nevertheless, it also cited several animal studies which show increased AL and lower burst pressures with both non-selective and selective NSAID use.

Neoadjuvant Radiotherapy

The findings from the Dutch Colorectal Cancer Group reported no significant difference in leak rates between the neoadjuvant radiotherapy arm (11%) and the no radiotherapy arm (12%) [28] which looked at short-course radiotherapy with 25 Gy. Regarding long-course chemoradiotherapy, an American group in 2012 reported on 1862 patients with no significant difference in leak rates in their chemoradiotherapy group vs their no radiotherapy group (8% vs 5.7% $p = 0.06$) [29]. This is in the context of lower tumour height in the radiotherapy arm (6.6 vs 9.7 cm $p < 0.001$).

Technical Factors

Stapled vs Hand-Sewn

A Cochrane review comparing stapled vs hand-sewn anastomoses for ileocolic resections, updated in 2011, reported AL rates of 2.49 and 6.1% respectively, with an OR 0.48 (0.24–0.95, $p = 0.03$) [30]. The leak rates for hand-sewn anastomoses are higher than expected and may reflect issues with reproducibility and perhaps familiarity with technique.

However with colorectal anastomoses, a separate Cochrane review in 2011 reported no difference in AL rates when comparing stapled to hand-sewn anastomoses.

Hand-Sewn Technique

A systematic review of six trials comparing single-layer (299 patients) vs two-layer sutured anastomoses (371 patients) showed no difference in AL rates [31]. This finding is supported by a Cochrane review of seven trials with similar findings [32]. The conclusion drawn supports a single-layer hand-sewn technique given the reduced operative time.

Colonic Pouch

A systematic review comparing colonic J-pouch and straight coloanal anastomoses reported a lower AL rates in the J-pouch group (RR 0.36, CI 0.12–1.08) [33]. This review covered eight randomised studies, and all but the largest study had no difference in leak rates. The largest study in 1996 by Hallbook reported AL rates of 1/45 (2.22%) of J-pouch patients and 8/52(15.3%) in the straight coloanal group skewing results in favour of J-pouches [34]. The advantages reported by these studies lie largely in better functional outcomes in the short term, with no measurable difference in stool frequency and function at 2 years.

Bowel Prep

Mechanical bowel preparation has been the subject of many systematic reviews and meta-analysis. A Cochrane review in 2011 and more recent review by Cao et al. in 2012 reported no difference in AL rates in the bowel prep group [35, 36]. Guenaga et al. in their review also compared mechanical prep to rectal enema with no significant difference in AL rates as well as infective complications in either group.

Drains

The role of prophylactic drains in colorectal surgery is controversial. A Cochrane review in 2004 of 1140 patients in six RCTs showed no difference in clinical- or radiology-detected leak rates in the drain vs no drain group [37]. However, a more recent meta-analysis by Rondelli et al. looking specifically at extraperitoneal colorectal anastomoses contradicts this finding for this subset of patients. The analysis included three RCTs and five non-randomised trials totalling 2277 patients, the odds ratio of AL in patients with a drain vs no drain being 0.42 (0.28–0.62) when all the studies were included [38]. The subgroup analysis of only the randomised trials (three) totalling only 291, however, showed no difference when drains were used.

Of note, a large series of 978 consecutive patients in Taiwan reported a significant increase in the rate of AL in their cohort with the use of suction irrigation drains [39].

Omentoplasty

Omental wrapping (omentoplasty) has been assessed in an old study in 1998 in a prospective randomised trial. This level 2 evidence showed no difference in AL rates, operative re-intervention and mortality between the two groups [40].

Intraoperative Leak Testing

Beard et al. in 1990 demonstrated in a randomised trial, a reduction in clinical AL with the introduction of intraoperative air leak tests from 14 to 4%. Radiologic leaks detected with routine contrast enema at day 10 reduced from 29 to 11% in the leak test group (66% of anastomoses were extraperitoneal) [41]. Eighteen (25%) patients had a demonstrable air leak which was repaired intraoperatively (method of repair not stated). Of these patients, one developed a clinical leak and two developed radiologic leaks.

In addition, Riccardi et al. described a series of 998 patients, 65 patients in whom an air leak was detected intraoperatively. The AL rate was 3.8% in those with no air leak and 7.7% in those who had a positive leak test. In patients with a positive test, suture repair alone 5/41 (12.2%) resulted in AL vs 0/14 patients with re-do of the anastomosis and 0/10 who underwent repair with faecal diversion [42].

Intraoperative Endoscopy

There are no studies comparing intraoperative endoscopy to a control group of no assessment. One group reported on a consecutive series of 73 patients, in whom 7 patients were found to have bleeding from the anastomosis site, managed by sutures, and 4 had positive air leak tests (2 suture repair and 2 re-do anastomoses) [43]. Similar findings were reported in a second series, which compared routine endoscopy to a selective endoscopic assessment of the anastomoses and found no difference in the two groups [44].

Role of Faecal Diversion

It has long been part of surgical teaching that faecal diversion does not prevent anastomotic leaks but reduces the magnitude of complications should a leak occur. Typically, low and ultralow anterior resections fall into this category, given the higher leak rates and the consequence that a leak at this level will likely render a restorative procedure impossible. This issue however is the subject of much controversy, as the evidence in the literature regarding the role of routine or selective faecal diversion is conflicting.

A 2010 Cochrane review of faecal diversion for anterior resections identified five RCTs. The meta-analysis determined that there was no difference in mortality between diverted and non-diverted patients. However, not surprisingly, the pooled data shows a risk ratio of 0.33 (0.21–0.53) for clinical anastomotic leak in the diverted group and lower rate of urgent reoperations (RR 0.28, CI 0.17–0.48) [45]. This finding is supported by a systematic review which also included non-randomised series [46].

However, a consecutive series of 1791 non-randomised patients, those undergoing a "low pelvic anastomosis" with covering stoma, had higher rates of renal failure postoperatively (1.7 vs 0.5% $p = 0.0485$) and no difference in septic complications [47].

Diagnosis

The early diagnosis and intervention in AL is essential in reducing the rates of morbidity and mortality. However, the diagnosis of AL can be difficult due to a wide spectrum of presentation. These can present radiologically as a subacute collection or free perforation peritonitis. A report on a consecutive series of 4019 patients with either contained or free AL presented with an average of three common symptoms, namely abdominal pain (64%), fever (52%) or nausea (24%). Eighty percent of patients also had non-specific findings on examination such as low-grade fever (> 38.6%), mild tachycardia (> 90%) or leukocytosis [48]. Only 22% reported frank peritonitis. In fact, surgical assessment alone has been reported to have a sensitivity as high as 91% but quite a low specificity of only 50% [49].

However, a study by Sutton et al. showed 15/22 patients with AL were initially misdiagnosed, with 13 (59%) of patients treated for cardiac symptoms, 1 (5%) for obstruction and 1 (5%) for ascites [50]. In diverted patients, up to 35% of patients with radiographically detected AL may be asymptomatic.

The average presentation of AL is typically between the fifth and eighth postoperative day. Attempts to detect AL earlier have led to the development of prospective scoring systems. One by den Dulk et al., which applies a score to a number of physiological parameters, reported an overall sensitivity of 97% for AL with a specificity of 53%. A simplified score looking at four parameters, respiratory rate > 20, clinical deterioration, presence of abdominal pain and C-reactive protein (CRP) > 250, has been prospectively evaluated with similar sensitivity and specificity and a negative predictive value (NPV) of 99.5% [51].

CRP

A recent systematic review of 2483 patients suggested that the CRP is a useful negative predictive test. The derived cutoffs for

CRP on postoperative days 3, 4 and 5 are 172, 124 and 144 mg/L respectively. These values corresponded to a NPV of 97%. It should be noted that the positive predictive value for these CRP readings was low ranging between 21 and 23% [52].

Imaging Techniques

The diagnosis of ALs is most commonly confirmed by CT scan with oral and/or rectal contrast or a contrast enema study which has been in use for over 30 years. However, Goligher in 1970 found that contrast enema was superfluous when compared to digital rectal examination [53]. This is in contrast to Nicksa et al. whose article reports that in patients with AL, 15/18 (83.3%) had a positive contrast enema compared to 4/27 (14.8%) who had a positive CT scan [54]. This improved to 33% if findings of air or free fluid in abdominal cavity on CT scan were taken into consideration rather than contrast extravasation alone.

Management

The International Study Group of Rectal Cancer has posed a grading system for AL [7].

- Grade A: Corresponds to radiological leakage not associated with any clinical symptoms or abnormal laboratory tests.
- Grade B: Require intervention non-operatively and this includes antibiotics and/or radiological drainage.
- Grade C: AL that requires re-laparotomy.

This grading system really reflects the clinical spectrum of AL, and in many respects, it is the clinical presentation that dictates how these leaks are managed. Management algorithms for the management of anastomotic leaks were proposed by the International Anastomotic Leak Study Group and will be outlined below [55].

Grade A leaks are often amenable to observation alone. These are typically the radiologic leaks detected on contrast enema performed prior to reversal of a diverting stoma.

Management of intraperitoneal Grade B leaks will be dictated by the patient's clinical picture. For large abscesses > 3 cm, the feasibility of percutaneous drainage would need to be considered, and if not possible, surgical drainage should be considered. Extraperitoneal Grade B leaks may be accessible by percutaneous drainage, but where this fails, transanal drainage often through the anastomotic dehiscence may control the infection. The evidence is scarce in this area, and techniques for achieving transanal drainage vary from simply opening the defect to allow drainage bluntly or with a formal surgical device, or with insertion of drains. Uses of newer devices, such as endoscopic vacuum-assisted closure, such as the Endo-Sponge™ have been described in 29 patients with AL with resolution occurring in 28/29 (96.5%) patients over an average of 34 days with 11 endoscopic sessions [56].

Grade C leaks with extensive peritoneal contamination require the anastomosis to be taken down. For a sigmoid or rectal anastomosis, this would equate to a Hartmann's colostomy. There are some reports of re-doing the anastomosis with proximal diversion, but this should be reserved for patients without symptoms of sepsis or other high-risk features. Patients with extraperitoneal ALs are of the group who are already diverted and often present with a subclinical or radiological leak; when symptomatic, they should be considered for a diverting stoma.

Outcomes

Anastomotic leaks result in significant morbidity and mortality. An Australian series of 1598 patients reported a mortality rate of 1.7% [10] in patients with a leak, but in other series, this can be as high as 29% [8, 57, 58].

Local recurrence rates after AL are higher, one study from the UK of 5173 patients reporting 5-year local recurrence rates after colorectal anastomoses in the order of 25.1% compared with 10.4% in the no leak group. Anastomotic leak remained a significant factor in local recurrence on multivariate analysis after adjusting for cancer stage [58]. It is postulated that viable cancer cells, present in the lumen of resected bowel, may then implant extraluminally.

Novel Techniques

Doppler Assessment

An older study from 1994 examined the use of Doppler ultrasound in assessing the vascularity of an anastomosis, reported a leak rate of 1% in a consecutive series of 200 patients. Ten patients had their anastomoses refashioned due to poor flow on ultrasound, the group citing that this may have contributed to their low AL rate [59].

A newer techniques using near-infrared spectroscopy to assess tissue oxygenation (StO_2) reported on a series of only 20 patients, 2 of whom had an AL. Both patients with AL had measures $StO_2 < 60\%$ compared with remaining 18 patients with $StO_2 > 66\%$. [60]

Drain Fluid Assessment

The use of drains has been discussed earlier. Nevertheless, there are several papers looking at the role of drain fluid analysis in predicting AL. These "biomarkers" attempt to facilitate the early diagnosis of AL, with the measurement of markers

that may reflect ischaemia (i.e. pH, lactate, pyruvate) or inflammation (i.e. IL-6, IL-10, TNF-α). Millan et al. tested pH at the anastomoses of 90 patients and found pH < 7.28, as their surrogate for ischaemia, in the first 24 h of surgery to be an independent risk factor for AL [61] with a sensitivity of only 28.1% and specificity of 98.3%.

Along similar lines, analysis of drain fluid content for IL-6, IL10 and TNF-α has been reported to be higher on day 3 in patients exhibiting AL [62].

Intraluminal Devices

Studies using intraluminal devices date back over 50 years from the use of rectal tubes, to purpose made silicone stents and colonic bypass tubes. There is a paucity of randomised studies for these devices to show their clinical utility, which limit their general uptake.

Ravo et al. first described the Coloshield™ in 1985 which is a silastic tube sutured with PDS to the bowel proximal to an anastomosis, essentially protecting the anastomosis from the faecal stream. As the sutures dissolve, the tube will be passed per rectally between days 15 and 30. In this series of 29 patients, there were no ALs [63]. There is no comparative study to a control group or diverting ileostomy group and the difficulties in placing it; the Coloshield™ has not gained widespread acceptance.

Newer devices such as the C-seal have a similar design but are comprised of a biodegradable material which is stapled along the colon in a colorectal anastomosis, with the sleeve then degrading and passing per rectally as it degrades. A series of 37 patients has been reported with a leak rate of 3% (one patient); however, three patients had perianastomotic collections which drained spontaneously; however, these were not classified as leaks. Despite the intraluminal device being used, 49% of patients still underwent diverting stomas [64].

Xiao et al. described transanal tube placement left in place for 5 days postoperatively reduced their AL rates in a prospective randomised trial with 200 patients in the transanal tube arm and 198 patients in the control arm. No diverting stomas were used in either arm with their primary endpoint being AL. Eight of 200 (4.0%) patients in the transanal tube group had AL, compared with 19/198 (9.6%) of the control arm [65].

Conclusion

ALs will forever pose challenges to the surgeon in diagnosis and management. It is often the yardstick by which each surgeon is measured. It is the source of significant morbidity to patients and health care services worldwide. Despite the evolution over the last several decades, new surgical staplers and techniques, robotic surgery and other anastomotic techniques, there has not been a decrease in ALs in colorectal surgery. As a result, a low threshold for investigation and intervention is mandatory to ensure better outcomes and lower overall mortality and morbidity.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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