Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks

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Background: Anastomotic leak (AL) represents a dreaded complication following colorectal surgery, with a prevalence of 1–19 per cent. There remains a lack of consensus regarding factors that may predispose to AL and the relative risks associated with them. The objective was to perform a systematic review of the literature, focusing on the role of preoperative, intraoperative and postoperative factors in the development of colorectal ALs.

Methods: A systematic review was performed to identify adjustable and non-adjustable preoperative, intraoperative and postoperative factors in the pathogenesis of AL. Additionally, a severity grading system was proposed to guide treatment.

Results: Of 1707 papers screened, 451 fulfilled the criteria for inclusion in the review. Significant preoperative risk factors were: male sex, American Society of Anesthesiologists fitness grade above II, renal disease, co-morbidity and history of radiotherapy. Tumour-related factors were: distal site, size larger than 3 cm, advanced stage, emergency surgery and metastatic disease. Adjustable risk factors were: smoking, obesity, poor nutrition, alcohol excess, immunosuppressants and bevacizumab. Intraoperative risk factors were: blood loss/transfusion and duration of surgery more than 4 h. Stomas lessen the consequences but not the prevalence of AL. In the postoperative period, CT is the most commonly used imaging tool, with or without rectal contrast, and a C-reactive protein level exceeding 150 mg/l on day 3–5 is the most sensitive biochemical marker. A five-level classification system for AL severity and appropriate management is presented.

Conclusion: Specific risk factors and their potential correction or indications for stoma were identified. An AL severity score is proposed to aid clinical decision-making.

Introduction

Anastomotic leak (AL) remains one of the most detrimental complications, accounting for considerable morbidity and/or mortality[1,2]. The annual direct healthcare costs are £1·1–3·5 million (€1·4–4·4 million; exchange rate 21 October 2014) in the UK alone, whereas in the USA the cost is over US $24 000 (€18 700) per patient[3,4]. The prevalence of AL varies from 1 to 19 per cent according to anatomical site (*Table 1*)[5–15], preoperative, intraoperative and postoperative factors. The highest leak rates occur with extraperitoneal anastomoses.

The definition of AL is widely agreed as a breach in a surgical join between two hollow viscera, with or without active leak of luminal contents (although there are some minor derivations)[16]. The term encompasses a wide

Table 1 Anastomotic leak rates from selected series

Anastomosis type	Leak rate (%)
Enteroenteric[5,6]	1–2
Ileocolic[6–10]	1–4
Colocolic[7,9–11]	2–3
Ileorectal[6,9]	3–7
Colorectal/coloanal[6,7,10,12,13]	5–19
Ileoanal pouch[14,15]	4–7

spectrum of clinical severity, ranging from small, contained leaks without systemic symptoms to widespread peritoneal contamination with accompanying severe sepsis, multiple organ failure and/or death.

A systematic review[17] of 97 papers identified 56 different definitions of AL, of which 29 related to the lower

gastrointestinal tract. It illustrated that terms and definitions used to describe AL are fundamentally muddled in the literature, hindering the ability of surgeons to compare studies effectively. There was huge variability in the terminology used, such as leak, breakdown, insufficiency, disruption, early, controlled and late leak. In addition, some of the grading terms used included partial, occult, complete, overt, covert, trivial and contained symptomatic leaks. When diagnosing a leak two common phrases are used, radiological and clinical, which makes it difficult to compare studies. The review emphasized the importance of comparing like with like when discussing AL.

To date there remains no clear consensus or international guidelines pertaining to the definition of AL. The aim of this review was to highlight the current best evidence for surgical practice and decision-making with regard to the prevention and diagnosis of AL. A five-level classification system for AL severity with management options is presented as well as areas for future research.

Methods

A systematic literature review was performed according to guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA)[18].

Search strategy

An electronic search of MEDLINE from PubMed, Embase and the Cochrane Library was carried out. The keywords 'colonic', 'colon', 'rectal', 'rectum' 'anastomosis', 'anastomotic', 'leak' and 'leakage' were sought without date restriction. All titles were screened and appropriate abstracts reviewed. The last search date was 18 May 2014.

Inclusion criteria

To be included in this review studies must have reported on: AL, colorectal surgery and human studies, in the English language.

Exclusion criteria

Excluded were: articles not pertaining to colorectal ALs, studies with fewer than 200 patients, overlapping studies, case reports, reviews, consensus statements and opinion articles.

Extraction process

The search was performed independently by two reviewers; a third author arbitrated any disagreements on inclusion
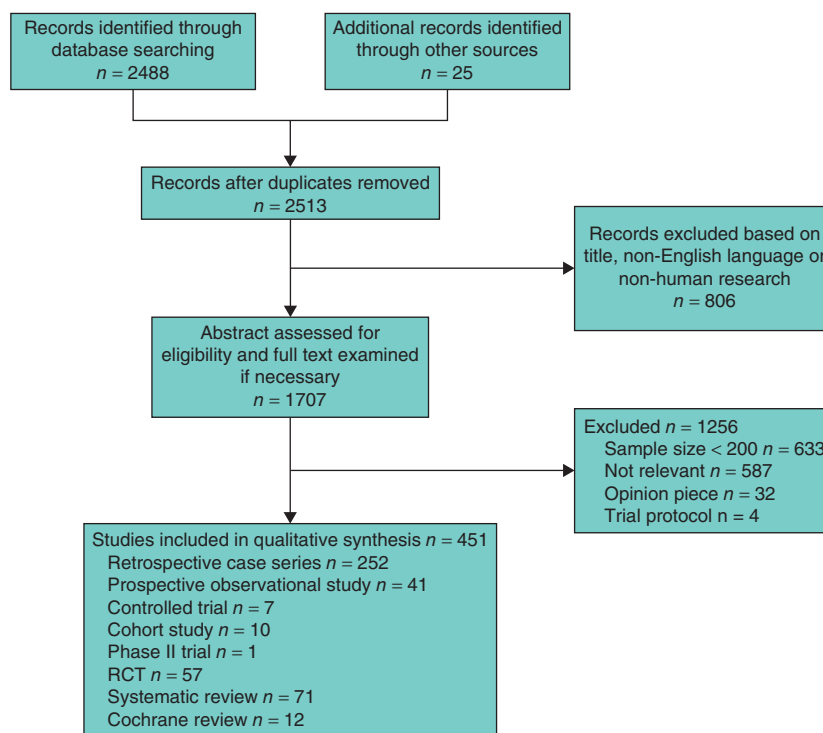

Fig. 1 Selection of articles for review. RCT, randomized clinical trial

or exclusion of studies. Included papers and results were entered into a standardized database with removal of duplicates. Further studies were identified by manual searches of reference lists of the relevant studies found.

Outcomes of interest

Preoperative, intraoperative and postoperative factors were extracted and used to compare AL rates. Diagnostic tools and scoring/grading systems for ALs were also evaluated.

Statistical analysis

Descriptive statistics were used to report and compare data in all studies. $P < 0.050$ was deemed significant and effect sizes are presented with 95 per cent c.i.

Literature review results

The initial search produced 2513 papers. Following screening of titles, removal of duplicates, non-English-language and non-human papers, 1707 papers were assessed based on the abstract and full text if necessary. Some 451 studies were finally included in the review (*Fig. 1*). Preoperative and intraoperative risk factors for AL are summarized in *Table 2*.

Preoperative risk factors

Although accurate prediction of risk is impossible, certain factors are known to influence AL rates. Appreciation of these factors may help surgeons to optimize patients before surgery, including selection of those who would benefit from either a diverting stoma or a decision to avoid anastomosis at all. Factors including male sex, age, smoking, neoadjuvant radiotherapy, obesity, location of tumour and immunosuppression have all been reported as being associated with increased AL risk.

Non-adjustable risk factors

Sex

Men have been shown to have an increased risk of AL across all types of colorectal anastomosis[19–24], rectal anastomoses alone[25–30], and similarly in a large series[31] of almost 1000 colocolonic anastomoses. The sex difference may be explained in part by an anatomical difference in the form of a narrower male pelvis[30] and the influence of hormone-related differences in intestinal microcirculation[32].

Table 2 Preoperative and intraoperative risk factors

Preoperative	Intraoperative
Non-adjustable risk factors	Increase risk
Male sex	Intraoperative contamination
Distal anastomosis, particularly rectal	Duration of surgery > 4 h
Tumour size > 3 cm	Inotropes
Advanced tumour stage	Blood loss
Metastatic disease	Blood transfusion
History of radiotherapy	Reduce risk
ASA fitness grade > II	Preoperative antibiotics
Diabetes	(intravenous and
Pulmonary disease	selective decontamination of
Vascular disease	digestive tract)
Renal disease	Cardiac monitoring/goal-
Emergency surgery	directed fluid management
Ex-smoker (> 40 pack-years)	Stapled anastomosis for right
Potentially adjustable risk factors	hemicolectomy
Smoking	
Obesity (high BMI/waist : hip ratio/visceral fat)	
Alcohol excess (> 21 units or 105 g alcohol per week)	
Corticosteroids	
Biological agents in combination with corticosteroids	
Bevacizumab	
Malnutrition/hypoalbuminaemia	
Contentious	
Preoperative radiotherapy	
Experimental evidence for mycophenolate mofetil, tacrolimus, everolimus	

ASA, American Society of Anesthesiologists; BMI, body mass index.

Age

Increasing age is no longer seen as a contraindication to colorectal surgery, with numerous studies reporting excellent outcomes in the elderly[33,34], who have further benefited from laparoscopic surgery[35]. However, a series[26] of 1391 patients undergoing rectal surgery suggested that age over 60 years remains an independent risk factor for AL (hazard ratio 2·52). Despite several publications[36,37] stating that age is a contributing risk for AL, there is a lack of strong statistical evidence to prove this categorically.

Previous history of radiotherapy

Anastomosis should be performed using healthy bowel, which can be challenging in patients who have received radiotherapy, for example pelvic irradiation for cervical cancer. Patients undergoing bowel anastomosis for chronic radiation enteritis have AL rates as high as 36 per cent, with an associated mortality rate of 21 per cent[38]. Although the management of radiation enteritis is a complicated subject and cannot be covered in sufficient detail within the remit

of this review, the operating surgeon should consider a previous history of irradiation when considering whether anastomosis can be undertaken safely.

American Society of Anesthesiologists fitness grade

American Society of Anesthesiologists (ASA) fitness grade of at least II[39], III[1,40,41] or IV[29,42] has been independently associated with an increased risk of AL. A study[42] of over 500 patients who underwent colorectal anastomosis found that the role of ASA score was greater than that of the Charlson co-morbidity index in predicting AL.

Underlying disease

Pre-existing diabetes mellitus is an independent risk factor for AL in ileocolic anastomoses[40,43]. Although another publication[44] suggested there was no increased AL risk, diabetic patients with an AL had a much higher mortality rate (26·3 per cent *versus* 6·0 per cent in non-diabetics). Underlying pulmonary disease[45−47] and pre-existing vascular disease[48] are both independent risk factors for AL in rectal resection. Renal disease is associated with a higher risk of AL. Patients receiving renal replacement therapy or those on immunosuppression with a transplanted kidney have higher AL rates, particularly if the procedure is performed as an emergency[49,50]. Preoperative and postoperative dialysis reduces risks, and the bowel should be defunctioned in operations performed as an emergency[49,51,52].

Emergency surgery

Emergency resection is an independent factor for AL (relative risk 4·6, 95 per cent c.i. 1·9 to 9·8)[53]. The presence of peritonitis and/or bowel obstruction is also predictive of AL. There is an abundance of literature, including systematic reviews and one randomized clinical trial (RCT), on the feasibility of anastomosis with a defunctioning stoma for peritonitis due to perforated diverticulitis[54−56]. Anastomosis is not necessarily contraindicated in emergency circumstances. One RCT[56] closed early owing to low accrual, but early results suggested lower complication rates and a higher rate of stoma reversal in patients undergoing restorative (covered with a loop stoma) *versus* non-restorative (end stoma) surgery. Judicious use of a temporary proximal stoma or avoidance of an anastomosis are sensible and safe options where there are any concerns. AL risk is cumulative based on the patient's risk factors. For example, an emergency resection with significant blood loss needing transfusion in a patient with co-morbidities requiring inotropes has such a high risk of leak that anastomosis is contraindicated.

Tumour features

It is widely accepted that the risk of AL increases with more distal anastomoses[1,20,57]. Several studies have reported an increased incidence of AL in rectal procedures compared with more proximal anastomosis. Furthermore, for rectal procedures the distance from the anal margin is a significant predictor of AL[13,19,21−23,25,26,28,29,39,43,48,58−61], with the risk increasing the closer the tumour is to the anal margin. Tumour size has been analysed infrequently as a contributing factor to AL. Some studies have demonstrated that tumour sizes greater than 3 cm[62] or 4 cm[29] are independently predictive of AL. Advanced neoplastic stage is also a risk factor for AL[19,48,57]. Using multivariable analysis, Richards and colleagues[63] found that metastatic disease at the time of anterior resection increases the risk of AL (odds ratio (OR) 3·43, 95 per cent c.i. 1·38 to 9·82).

Adjustable risk factors

Smoking

Active smokers have a higher risk of AL[20,28,63−65]. Several studies have reported current smoking status as an independent risk factor. Additionally, previous heavy smoking may be a risk factor for AL[66].

Obesity

Several studies[40,67−69] have shown obesity to increase the risk of AL. Alternatives to body mass index (BMI), such as waist circumference and waist to hip ratio, may predict AL risk (univariable analysis: OR 13·7; relative risk 3·3, 95 per cent c.i. 1·2 to 9·2)[70]. Indeed measuring visceral fat area is more sensitive than BMI, especially following laparoscopically assisted colectomy[71]. This implies that visceral fat, rather than obesity in general, carries a risk of AL (as well as metabolic syndrome, hypertension, diabetes, etc.).

Alcohol

Excessive alcohol consumption is an important predictive factor for AL. Multiple regression analysis has shown that heavy alcohol intake (over 21 units weekly) is associated with AL (relative risk 7·18, 95 per cent c.i. 1·2 to 43)[72].

Neoadjuvant (chemo)radiotherapy

Preoperative radiotherapy to downstage or downsize rectal tumours reduces local recurrence rates. Preoperative radiotherapy with or without concomitant chemotherapy was thought to be a risk factor for AL in retrospective studies[19,23,24,27,48]. However, prospective trials and cohort

studies as well as larger retrospective series have contradicted this, suggesting that neoadjuvant chemoradiotherapy does not influence AL rates[29,64,73]. The Medical Research Council (MRC) CR07 RCT[74] found no difference in AL between patients undergoing anterior resection who received either preoperative radiotherapy or selective postoperative chemoradiotherapy: 9 (95 per cent c.i. 6 to 12) and 7 (4 to 9) per cent respectively. Similarly, the Dutch total mesorectal excision (TME) trial[75] demonstrated no difference in AL rate between those undergoing preoperative radiotherapy and TME *versus* TME alone (11 *versus* 12 per cent). In patients with rectal cancer, there is no difference in AL rates between patients receiving chemoradiotherapy or not (7·5 *versus* 5·9 per cent)[76], suggesting that preoperative chemoradiotherapy is not a risk factor for AL.

Medications (immunosuppressants and chemotherapy)

In recent decades the proportion of patients on immunosuppressive or immunomodulating medications has increased. Prolonged use of corticosteroids may be a risk factor for AL, particularly when combined with other immunosuppressants or in cushingoid patients[45,46,77,78]. A systematic review[79] found an AL rate of 6·8 per cent in the corticosteroid group compared with 3·3 per cent in patients not treated with corticosteroid, but the duration and dose of treatment were heterogeneous. Infliximab alone may not alter AL risk, but in combination with other immune modulators can slow healing[80,81]. There is evidence to suggest that mycophenolate mofetil[82], ciclosporin A[83], tacrolimus[84] and everolimus[85] all increase the risk of AL. This comes from experimental studies, but patients with renal transplantation and immunosuppression do have higher AL, morbidity and mortality rates[49,50]. Azathioprine was shown to increases the risk of AL in one paper published in abstract form[86], but this has been contradicted by several other studies[87].

Recent use of chemotherapy, antiangiogenic and antimitotic agents also increases the risk AL. For example, bevacizumab (a vascular endothelial growth factor inhibitor) reduces neovascularization and healing. Bevacizumab has a half-life of 20 days; the manufacturers recommend stopping treatment at least 28 days before surgery, not restarting for at least 28 days afterwards and only when the wound has healed[88]. Some advocate a longer interval of 60 days without treatment before surgery is considered[89].

Nutrition

Patients undergoing right hemicolectomy who have experienced preoperative weight loss of more than 10 per cent have an increased risk of AL[90]. In over 72 000 rectal resections, Kang and co-workers[91] showed that preoperative weight loss and malnutrition, along with fluid and electrolyte disturbances, were associated with a higher risk of AL[91]. Several large series[29,92–94] have identified hypoalbuminaemia (albumin level below 3·5 g/dl; OR 2·56) as an independent predictor of AL and sepsis.

Mechanical bowel preparation

Several randomized trials have found that omitting mechanical bowel preparation (MBP) does not increase the risk of colorectal AL[95–98]. A systematic review[99] including over 5000 patients found no evidence that patients benefit from MBP (either orally or by enema)[99]. Although one trial[100] suggested that the morbidity rate was lower with MBP (restorative rectal cancer surgery), there was no difference in AL. Naturally, there are some advantages to MBP (such as facilitation of intraoperative endoscopy and stapler insertion), but its use remains an individual choice rather than an evidence-based mandate.

Antibiotics

The use of perioperative intravenous antibiotics is routine in emergency and elective colorectal surgery worldwide[101,102]. Prophylactic antibiotics are ideally given in advance of skin incision (ideally 30–60 min beforehand to achieve steady-state pharmacokinetics)[103]. Combining preoperative selective intestinal decontamination with oral antibiotics and perioperative intravenous antibiotics reduces surgical-site infections and may lower AL rates[103–105]. A meta-analysis[104] of eight RCTs comparing selective decontamination of the digestive tract with systemic antibiotics alone demonstrated an AL rate of 3·3 and 7·4 per cent respectively ($P = 0.002$).

Intraoperative risk factors

Operative technique has a substantial impact on healing and postoperative complications including AL. Emphasis on avoiding tension, with good apposition of tissues, is of key importance. The technical aspects are beyond the scope of this study but there are perioperative interventions that may influence anastomotic healing. Intraoperative contamination or dirty wounds[78] and duration of operation exceeding 4 h[1,78,106] are risk factors for AL.

Hypothermia increases the risk of surgical-site infections and induces vasoconstriction[107], but there is no conclusive evidence that it is a risk factor for AL. Hyperoxia (fraction of inspired oxygen 80 *versus* 30 per cent) reduced AL rates

in open infraperitoneal colorectal anastomoses in a small RCT[108], and appears to confer a reduction in mortality[109].

The use of inotropes is associated with a threefold increase in AL; this risk is accentuated by the use of multiple agents and duration of inotropic support[110]. This risk is independent of medical status as determined by Acute Physiology And Chronic Health Evaluation (APACHE) II and Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) physiological scoring systems. Hence, a diverting stoma should be considered in patients on inotropes if an anastomosis is performed.

Anaesthetic factors

Epidural anaesthesia

With the development of enhanced recovery protocols and emphasis on improved pain management, early mobility and judicious intravenous fluid management, anaesthetic factors contribute to a healthy patient and anastomosis. Epidural anaesthesia is commonly used in abdominal surgery and the initial concern that local anaesthetic epidurals would stimulate motility or increase AL risk was not based on strong evidence. A meta-analysis[111] of 12 small randomized trials suggested that epidurals contribute to AL risk. In contrast, Swedish rectal cancer registry data[39], one systematic review[112] and a recent retrospective analysis[113] of 4000 patients receiving epidurals have demonstrated that epidurals do not increase AL rates, or that any impact is small[112].

Fluid replacement

Intraoperative fluid management is an area of debate in the enhanced recovery era, with limited evidence regarding fluid management protocols. A randomized trial[114] comparing a restrictive *versus* liberal fluid regimen showed that the restrictive group had improved outcomes in terms of reduced pulmonary complications, but overall morbidity in this group was higher. There have been several studies on this topic; those that quoted AL rates reported no difference between restricted *versus* liberal fluid administration[115−118]. Published studies lack consistency in terms of definitions, methodology and patient groups. Many trials excluded patients with co-morbidities (for example ASA grade III and above) and their applicability to an unselected cohort of surgical patients is therefore unclear[119]. There is a trend towards goal-directed therapy to individualize fluid management, with the assistance of cardiac output monitoring, including the use of oesophageal Doppler monitoring. Meta-analyses[120,121] have demonstrated reduced complications in major abdominal surgery with the use of

oesophageal Doppler monitoring; on that basis it is recommended by the National Institute for Health and Care Excellence[122] for major colorectal surgery, but has not been shown to reduce AL rates.

Anastomosis

Formation of anastomosis

An RCT[123] of 732 patients comparing sutured with stapled colorectal anastomosis found a significantly increased rate of radiological leaks in the sutured group, but no difference in clinical leaks. Stapled anastomosis was associated with a lower rate of tumour recurrence and cancer-specific mortality. The authors concluded that, although both techniques are safe, there is a long-term benefit of stapling anastomoses in patients with colorectal cancer. When comparing use of sutured *versus* stapled anastomoses it is imperative to compare similar anatomical locations owing to differences in blood supply, luminal diameter and type of reconstruction. Newer techniques such as metallic compression ring anastomoses have been developed, which have proven to be effective in feasibility studies with comparable AL rates, but more evidence is required[124,125].

Ileocolic anastomosis

Kracht and colleagues[8] randomized patients with right-sided colonic cancer to stapled side-to-side or four types of handsewn ileocolic anastomosis. There was a significantly reduced AL rate of 2·8 per cent for stapled anastomoses, compared with 8·3 per cent for the handsewn techniques combined. The authors concluded that, although more costly, side-to-side stapled anastomosis should be favoured for right hemicolectomies for carcinoma. This has been the subject of several Cochrane reviews comparing stapled with sutured anastomoses, the most recent in 2011[126]. Seven trials (one unpublished) including 441 stapled and 684 handsewn anastomoses were analysed. Although none of the individual trials demonstrated a significant difference between the techniques, the overall meta-analysis favoured stapled anastomosis, with an AL rate of 2·5 per cent, compared with 6·1 per cent for handsewn anastomoses (OR 0·48, 95 per cent c.i. 0·24 to 0·95; $P = 0·03$). In subgroup analysis of patients with cancer, stapled anastomoses had lower AL rates (1·3 *versus* 6·7 per cent; OR 0·28, 0·10 to 0·75; $P = 0·01$). One study[127] looked solely at ileocolic anastomosis in Crohn's disease but the numbers were insufficient to allow a conclusion to be reached for anastomoses in this disease.

Anterior resection

Popularization of circular staplers 30 years ago meant that some patients with mid and low rectal tumours that were

previously treated by abdominoperineal resection could be offered an anterior resection. A Cochrane review[128] in 2012 compared the use of sutures *versus* stapling devices for anterior resection; nine trials were included, with 1231 patients. No superiority was found for either technique, including AL rates. However, the review highlighted that resections of rectal and more distal tumours were associated with a greater risk of AL.

Other factors

Defunctioning stoma

Following construction of an anastomosis, particularly in low and ultralow anterior resections, a large proportion of surgeons create a defunctioning stoma to divert the faecal stream. This is not to prevent AL, but rather to reduce the sequelae should an AL occur. The most commonly used form of stoma is the defunctioning loop ileostomy, but some surgeons advocate the use of loop colostomies. Four RCTs have compared outcomes of patients undergoing anterior resections with or without defunctioning stomas; two[129,130] solely used ileostomies, one[131] used loop ileostomy or transverse colostomy, and the other[132] solely colostomies. Matthiessen and co-workers[131] demonstrated a symptomatic leak rate of 10·3 per cent and a significantly lower reoperation rate in the defunctioned group (ileostomy or colostomy), compared with 28 per cent in the non-stoma group, in a cohort of 234 patients. Similar results were obtained in a slightly larger study[129] of 256 patients with low rectal cancer, which demonstrated significantly reduced AL rates in the group with a defunctioning ileostomy (2·3 *versus* 9·3 per cent); no patient in the ileostomy group required surgical intervention or died. Finally the most recent RCT[130] studying use of a defunctioning stoma in patients low rectal cancer terminated early after recruiting only 40 patients, as the leak rate was 5·5 per cent in the defunctioned group compared with 37·5 per cent in the group with no stoma. Several meta-analyses have compared ileostomies with colostomies; the most recent[133] included five RCTs and seven non-randomized trials, with a total of 1687 patients. This meta-analysis marginally favoured ileostomies, owing to a reduced incidence of stoma prolapse and wound infection[134], but there is a lack of high-quality RCTs and most studies were underpowered.

Blood supply, blood loss and transfusion

Several studies and meta-analyses have investigated the level of vessel ligation and its relationship to AL[135,136]. The evidence is contradictory as the majority of studies concern elective sigmoid resections for diverticular disease, and their findings may not be applicable to cancer.

A meta-analysis[137] including four studies with 400 patients demonstrated a lower (but not statistically significant) leak rate in the 'low-tie' group than in the high-ligation group (7·3 *versus* 11·3 per cent respectively). The advent of TME has reduced local cancer recurrence and prolonged survival, but at the risk of greater disruption of the blood supply to the rectal part of the anastomosis[138–141].

Blood loss greater than 100 ml[142] and multiple blood transfusions[106] are both independent risk factors for AL, but whether this is a specific manifestation of the consequences of blood loss or whether blood loss is a surrogate for poor operative technique or challenging surgery is unclear.

Laparoscopic versus open surgery

The benefits of laparoscopic surgery are now accepted widely and the evidence base is growing, but patient selection is essential. RCTs confirming equivalent oncological outcome and long-term survival between open and laparoscopic surgery have been published[143,144]. The MRC Conventional *versus* Laparoscopic-Assisted Surgery in patients with Colorectal Cancer (CLASICC) trial[144] demonstrated leak rates of 3 and 4 per cent respectively for open and laparoscopic colonic resections; for rectal resections the respective rates were 7 and 8 per cent. Meta-analysis[145] of open *versus* laparoscopic rectal resections demonstrated no differences in AL rates, although the majority of the included papers were of poor quality. Similarly in rectal cancer resections following chemoradiotherapy, there was no difference in leak rates and circumferential resection margin positivity between open and laparoscopic procedures[146,147]. Laparoscopy does have distinct differences from open surgery, such as the need for multiple stapler firings when transecting the rectum, which is associated with an increased AL rate, although this is likely to be reduced with advances in stapler technology[19,148]. Laparoscopic resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable[149].

Omentoplasty

It has been suggested that wrapping gastrointestinal anastomoses in a well vascularized omentum may enhance healing or potentially contain small leaks, but efficacy remains unclear. For colorectal resections the evidence includes an RCT[150] of 705 patients that showed no difference in leak rate or severity, and a small meta-analysis[151] of three RCTs again demonstrating no difference. Interestingly, an RCT[152] of 126 patients undergoing rectal anastomosis demonstrated a significant reduction in leak rate among

patients with an omentoplasty (6·4 *versus* 21·9 per cent), although this study was criticized for being underpowered. There were also fewer reoperations and reduced mortality in the omentoplasty group. In another RCT, Tocchi *et al.*[153] found similar rates of staple-ring disruption in rectal anastomoses in both groups, but significantly lower clinical leak rates in the omentoplasty group. Although it is not always technically feasible and the evidence is not strong enough to recommend omentoplasty in all patients, this technique does not appear to be harmful and may help fill dead space in the pelvis following resection, along with the potential to contain small leaks.

Drains

The use of drains in intraperitoneal and extraperitoneal anastomoses has been debated widely in terms of early identification of complications, as well as preventing or lessening their impact. The use of drains for colorectal anastomoses was the subject of a systematic review[154] in 2006 including six RCTs. This review analysed data from 1140 patients and found no significant difference in AL rates or any of the other primary endpoints, concluding that there was insufficient evidence to support routine drainage. This confirms the findings of an earlier systematic review[155] of 13 RCTs, which concluded that most lower gastrointestinal operations with anastomosis can be performed without drainage. However, a recent meta-analysis[156] of drains in rectal cancer surgery demonstrated a reduction in AL rate with pelvic drainage (OR 0·51, 95 per cent c.i. 0·36 to 0·73). The current evidence does not support drainage of colonic anastomoses, but the case for drains for extraperitoneal anastomoses is less clear.

Air-leak testing

There remains no consensus on air-leak testing of colorectal anastomoses. Some surgeons advocate its routine use for anterior resections, by filling the pelvis with warmed saline and insufflating the rectum with air. However, practice varies if the air-leak test is positive. Should the anastomosis be taken down and redone, or does a suture repair with or without a diverting stoma suffice? Interestingly, the surgeons who advocate its use for anterior resections do not necessarily use the air-leak test for other gastrointestinal anastomoses, with the majority of publications focusing only on left-sided resections. The available evidence is in support of air-leak testing; in an RCT[157], AL rates were 4 per cent in patients who underwent air-leak testing *versus* 14 per cent in those who did not. A cohort study[158] including 998 patients, of whom 825 had an air-leak test, reported a positive test in 7·9 per cent. Clinical leaks were noted in 7·7 per cent of patients who had air leaks compared with 3·8

per cent who did not. Of note, the highest clinical leak rates occurred in patients with a positive air-leak test who had suture repair alone (12·2 per cent); rates were zero among patients who had faecal diversion or reanastomosis. Furthermore, a study[159] in 2011 demonstrated a trend towards lower leak rates with air-leak testing; however, the study was underpowered.

Other tests for anastomotic leakage

Other techniques such as intraoperative endoscopy[160], measuring local tissue oxygenation[161] and near-infrared spectroscopy[162] have been advocated with some promising results, but these techniques are experimental at present[163,164].

Postoperative factors

Medications

A large meta-analysis[165] analysed six RCTs that evaluated perioperative non-steroidal anti-inflammatory drug (NSAID) use in colorectal resections, and found no statistically significant effect. However, non-selective NSAIDs and non-selective cyclo-oxygenase 2 inhibitors were found to be associated with a higher AL rate by Gorissen and colleagues[166], whereas Holte and co-workers[167] and Klein *et al.*[168] showed that the incidence of AL increased significantly if patients were using celecoxib or diclofenac respectively. Thus, although the evidence is only circumstantial, NSAIDs should be used with caution in the postoperative period. This represents a topic that could be investigated further with an adequately powered RCT in the context of an enhanced recovery protocol.

Presentation and diagnosis of anastomotic leaks

The symptoms and signs associated with AL are difficult to discriminate from those of other postsurgical septic phenomena and so clinicians must be alert to the subtle signs, especially in the early stages of leakage. These include cardiac complications, such as atrial fibrillation, higher than expected inflammatory indices, and non-specific failure of the patient to thrive[169,170].

Delayed diagnosis of AL is associated with poorer outcomes, particularly after postoperative day 5[171]. ALs are associated with higher cancer recurrence and mortality rates[11,172]. One study[173] demonstrated that hospital stay including a weekend or negative imaging led to a delay in diagnosis of more than 2 days overall. It is therefore imperative to have a high level of suspicion, to aid early detection of AL[169]. Early diagnosis and appropriate treatment is integral to improving outcomes.

Inflammatory and biochemical markers

Monitoring of inflammatory markers following colorectal surgery augments clinical observation. This is particularly relevant in the era of enhanced recovery protocols, with earlier discharge from hospital after surgery. C-reactive protein (CRP), an acute-phase protein, has a half-life of 19 h; this and white cell count (WCC) constitute the most commonly used markers of postoperative inflammation and infection. CRP level has been used with variable success as an indicator of AL. One study[174] of 129 patients found that it was not a good test for discriminating between AL and other septic complications, but that a level of over 200 mg/l was at its most sensitive on day 3 after surgery (sensitivity 68 per cent, specificity 74 per cent). A meta-analysis[175] of 2483 patients (7 studies) demonstrated the median day of diagnosis for AL was day 6–9 and that CRP levels of over 172, 124 and 144 mg/l were the derived levels for AL for postoperative days 3, 4 and 5 respectively (negative predictive value 97 per cent). A recent study[176] reported that neither postoperative CRP nor procalcitonin level was useful for discriminating minor septic complications, but that they could sensitively predict major AL (requiring relaparotomy) on days 3–5 after operation. In summary, CRP and procalcitonin are useful screening markers for major AL when levels are very high (CRP greater than 150 mg/l), whereas WCC is less useful[48]. Patients exhibiting signs of sepsis and high levels of CRP and/or procalcitonin on postoperative days 3–5 should be monitored closely, and be considered for imaging and intervention.

Several other biochemical markers of AL have been investigated, such as markers of ischaemia, inflammation, wound repair and bacterial contamination. Markers of ischaemia include monitoring pH changes, and measurement of lactate and pyruvate levels via microdialysis catheters close to the anastomosis[177,178]. In addition, inflammatory factors, such as cytokines, lysozyme, matrix metalloproteinases and culture of intra-abdominal bacteria, have been studied with some promising results, but remain of experimental rather than clinical interest[163].

Radiological identification of anastomotic leak

Early detection of an AL is vital to reduce the risk of associated morbidity and mortality from septic complications. If a patient is seriously unwell and a leak is suspected, further diagnostic tests are not always required. However, in some patients clinical signs are non-specific and radiological confirmation is sought to assess anastomotic integrity. The diagnostic dilemma and the desire to avoid an unnecessary return to theatre may delay both diagnosis and management.

The most common imaging techniques used are CT and water-soluble contrast enema. Varying rates of sensitivity and specificity have been reported in the literature for both methods, with sensitivity of CT between 14·8 and 57 per cent[179–182], and of water-soluble contrast enema between 52·2 and 83·3 per cent[179,180,183]. Bertoni and colleagues[184] reported a sensitivity of 100 per cent for AL when both modalities were used in combination, but this was before ileostomy closure and not in the acute early postoperative period. Explanations for high false-negative rates include timing of the investigations when imaging is performed before there is radiological evidence of anastomotic dehiscence, quality of the technique used, and the radiologist's experience. CT and contrast radiography have their respective limitations and may be more useful in combination. The addition of rectal contrast to CT improves sensitivity and should be considered[185]. The results of radiological examination need to be interpreted in a clinical context, and it is important to emphasize that the available data suggest that these investigations cannot reliably exclude an AL. Additional imaging techniques that aid in diagnosing ALs have been reported, including transvaginal ultrasonography[186]. Teeuwen *et al.*[187] showed that uptake of fluorodeoxyglucose following uncomplicated colorectal surgery was low, suggesting there may be potential for the use of PET as a diagnostic test for AL.

Scoring and grading systems

Risk assessment is a fundamental part of surgical decision-making. This assessment, in conjunction with patient choice, guides the optimal treatment plan. It also governs intraoperative decision-making, such as whether to undertake an anastomosis and other considerations, including use of defunctioning stomas.

Several different types of scoring and grading systems exist; these can be divided into those that predict, diagnose or grade the severity of an AL. The colon leakage score (CLS) was developed to aid surgeons in decision-making for defunctioning the bowel, and attempts to predict the risk of a leak before surgery by assessing 11 weighted patient and operative factors for left-sided colonic resection[188]. A score of 11 of 43 was associated with a 3 per cent risk of a leak, which was the authors' cut-off for a low- *versus* high-risk anastomosis. Other physiological and risk scoring systems are used in surgery, but the CLS is the only one employed solely for the purposes of predicting ALs.

Scoring systems have also been developed in an attempt to identify leaks in colonic and rectal surgery to reduce time to diagnosis. The 'Dutch leak' or DULK score, developed

Table 3 Severity grading and management of anastomotic leaks

Grade	Example/CT findings/ sepsis bundles	Clinical signs of peritonitis	Haemodynamic changes	Setting	Inotropes	Intervention
1	Deviated from expected course; biochemical abnormalities	No	None	Level 0 (ward), colorectal nursing	No	Observe drain/fistula output
2	Sepsis and ileus amenable to abscess drainage	No	None (or tachycardia rapidly responsive to treatment)	Level 0 (ward)	No	Antibiotics and TPN if needed
3	Sepsis with ileus; requirement for nasogastric drainage and urinary catheterization	Single quadrant	Persistent tachycardia but normotensive	Level 1 (ward with critical care input)	No	Careful observation, antibiotics, TPN; low threshold for laparotomy
4	Severe sepsis	Multiple quadrants	Tachycardia and hypotension	Level 2 (HDU)	+/−	Resuscitation and expedient laparotomy
5	Septic shock	Generalized	Tachycardia, hypotension and shock	Level 3 (ITU)	Yes	Resuscitation, intensive care and emergency laparotomy

TPN, total parenteral nutrition; HDU, high-dependency unit; ITU, intensive therapy unit.

in 2009, comprises 13 factors, with more than 4 points representing a positive test[189]. Using a multivariable logistic regression model, the authors identified the four factors with the highest association with leakage and refined the system to the modified DULK score[190]. The four components were: respiratory rate more than 20 breaths/min, clinical deterioration, abdominal pain (other than wound pain) and CRP level over 250 mg/l. It was concluded that both DULK and modified DULK scoring systems are useful for the diagnosis of clinically relevant ALs. However, the positive predictive values of the DULK and modified DULK score are only 16 and 17 per cent respectively. If the clinical suspicion of AL is low, the high negative predictive scores of over 97 per cent for both scoring systems have some merit, but the very low positive predictive value does not help support earlier positive diagnosis.

The International Study Group of Rectal Cancer[191] carried out an extensive literature search on the definition of AL, and grading of the severity of AL after anterior resection. The search identified 59 papers that defined AL, 14 of which described severity. From this, a simple grading system was proposed: A, no therapeutic intervention; B, requiring active intervention but no relaparotomy; and C, requiring relaparotomy. This grading system was validated in a recent study[192] of 746 patients undergoing sphincter-preserving resection of the rectum. The AL rate was 7·5 per cent (grade A, 16 per cent; grade B, 23 per cent; grade C, 61 per cent). Scoring systems are useful for clinical practice and for research purposes to ensure comparison of like with like. For these systems to be effective, they need to be simple, but also include enough data to be meaningful.

The authors of this review therefore propose a grading system with five grades, including factors such as the level of care required, from ward-based to intensive care and interventional/operative strategies (*Table 3*).

Future research

ALs remain a huge challenge despite many surgical and technological advances. Although controversial, there is evidence for improved outcomes with the creation of subspecialization and centralization of services in high-volume centres[193,194]. Furthermore, continued high-quality research is of paramount importance to reduce the risk and sequelae associated with ALs. Improved early identification aided by use of scoring systems and imaging is essential for the successful management of ALs.

Finally, more research focusing on intraoperative blood flow assessment, combined with goal-directed fluid therapy, is warranted. Collaboration between research units across the globe to power studies adequately will be the key to success in reducing the burden of this potentially catastrophic complication.

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Snapshot quiz

Snapshot quiz 15/4

Question: What is the longest appendix ever removed?

The answer to the above question is found on p. 488 of this issue of *BJS*.

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