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REVIEW

Integrated approach to colorectal anastomotic leakage: Communication, infection and healing disturbances

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Abstract

Colorectal anastomotic leakage (CAL) remains a major complication after colorectal surgery. Despite all efforts during the last decades, the incidence of CAL has not decreased. In this review, we summarize the available strategies regarding prevention, prediction and intervention of CAL and categorize them into three categories: communication, infection and healing disturbances. These three major factors actively interact during the onset of CAL. We aim to provide an integrated approach to CAL based on its etiology. The intraoperative air leak test, intraoperative endoscopy, radiological examinations and stoma construction mainly aim to detect and to prevent communication between the intra- and extra-luminal content. Other strategies including postoperative drainage, antibiotics, and infectious-parameter evaluation are intended to detect and prevent anastomotic or peritoneal infection. Most currently available interventions for CAL focus on the control of communication and infection, while strategies targeting the healing disturbances such as lifestyle changes, oxygen therapy and evaluation of metabolic biomarkers still lack wide clinical application. This simplified categorization may contribute to an integrated understanding of CAL. We strongly believe that this integrated approach should be taken into consideration during clinical practice. An integrated approach to CAL could contribute to a better understanding of the etiology of CAL and eventually better patient outcome.

Key words: Colorectal anastomotic leakage; Integrated approach; Prevention; Prediction; Intervention

Core tip: Colorectal anastomotic leakage (CAL) remains

the most dangerous complication after colorectal surgery. In this review, we propose an integrated approach for CAL, consisting of three major parts, communication, infection, and healing disturbances. This simplified categorization is based on the etiology of leakage and may contribute to our integrated understanding of CAL, and eventually facilitate an integrated approach to CAL and eventually better patient outcome.

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INTRODUCTION

Colorectal anastomotic leakage (CAL) still remains a frequent and dangerous complication after gastrointestinal surgery, occurring in 4%-33% of patients and contributing to one third of postoperative mortality[1]. An anastomotic defect causes leakage of colonic content into the abdominal or pelvic cavity leading to peritonitis, abscess formation or sepsis[2]. CAL substantially prolongs hospital stay - by one to two weeks - and increases medical costs by as much as $24000 within the first period of hospitalization, thereby approximately tripling the expenditure relative to that of normal recovery[3,4]. Moreover, CAL is identified as a risk factor for local recurrence of colorectal cancer and is reported to reduce long-term cancer specific survival[5]. The need for more effective strategies to prevent and detect CAL is undoubtedly urgent. Many previous studies have explored techniques targeting the prevention, detection and intervention of CAL, but little attention has been paid to the systematic categorization of these strategies. To this end, we aim to provide surgeons with an integrated understanding of these strategies by a categorization based on CAL etiology.

INTEGRATED ETIOLOGY

In research, many efforts have been devoted to identifying risk factors of CAL such as being male[6], smoking[7], alcohol abuse[7], obesity[8], a high American Society of Anesthesiologists (ASA) score[9], low level (*e.g.,* rectal) anastomosis[10], late tumor stage[6], urgent operation[9], increased blood loss[11], after-hours surgery[12], corticosteroids administration[13], and prolonged duration of surgery[14]. However, these risk factors seem to cover most patients, and thus do not contribute to the understanding of the etiology of CAL.

Doctors and researchers still do not understand the detailed etiology of CAL. In many previous studies, CAL was attributed to technical failure or ischemia[15,16], but neither of these seem to explain the whole mechanism[17]. This emphasizes the need for an integrated approach regarding the etiology of CAL.

Based on previous literature and our investigations, we categorized the etiology of CAL into three major components: communication, infection, and healing disturbances (Figure 1).

Communication represents the classic definition of CAL: "communication between the intra- and extra-luminal compartments of the anastomotic bowel"[2]. Infection indicates bacterial infection at the anastomotic site, which is usually shown as anastomotic abscess or peritonitis. Healing disturbances represent pathological factors that may cause delay in wound healing.

We propose these three major components mainly due to two reasons. First, based on our observations and previous studies, evidence regarding these three aspects was always observed in patients with leakage such as lower anastomotic bursting pressure, anastomotic abscess, peritonitis, ischemia or anastomotic hypoxia[18-21]. Second, we also found that at least one of these factors can be identified as the main cause in CAL cases, which may also cause the other two as these factors actively interact with each other. For instance, it is known that severe infection significantly reduces organ perfusion[22], which may further worsen the healing process of the anastomosis, resulting in CAL. Furthermore, bacterial endotoxins activate the inflammatory response and cause infiltration of inflammatory cells, including subtype-I macrophages, which produce nitric oxide by inducible nitric oxide synthase (iNOS)[20,23]. This overexpression of iNOS is associated with a decrease in collagen deposition[24,25], which eventually causes a delay in wound healing and subsequent communication between intra- and extra-luminal bowel compartments.

PREVENTION

Nowadays, several techniques are available which could contribute to the prevention of CAL. In previous studies, surgeons and researchers have often categorized these strategies based on the time of application (*e.g.,* preoperative, intraoperative and postoperative)[26]. In addition to that, we divided these strategies into the three proposed categories, which further reveals their underlying mechanism (Figure 2).

Prevent communication

Many preventive strategies aim to prevent communication between intra- and extra-luminal compartments of the anastomosis.

The air leak test (ALT) is most frequently used as an intraoperative test in colorectal surgery to identify a technically failed anastomosis, which may cause direct communication between intra- and extra-luminal compartments. The rate of this intraoperative test varies greatly in studies evaluating the ALT[27]. Surprisingly, our

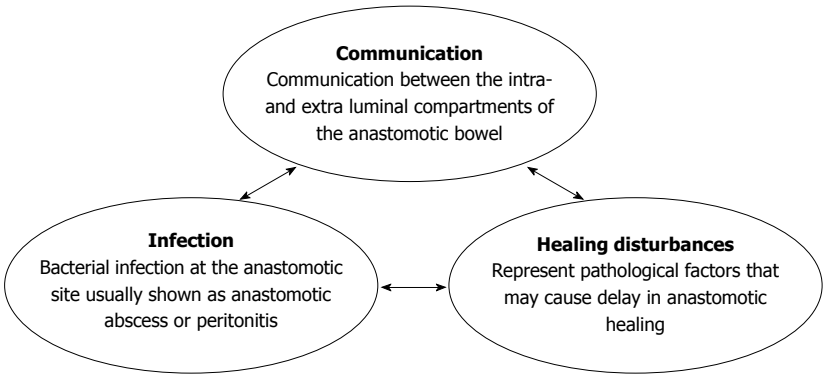

Figure 1 Integrated approach with proposed categorization based on the etiology of colorectal anastomotic leakage (communication, infection and healing disturbances).

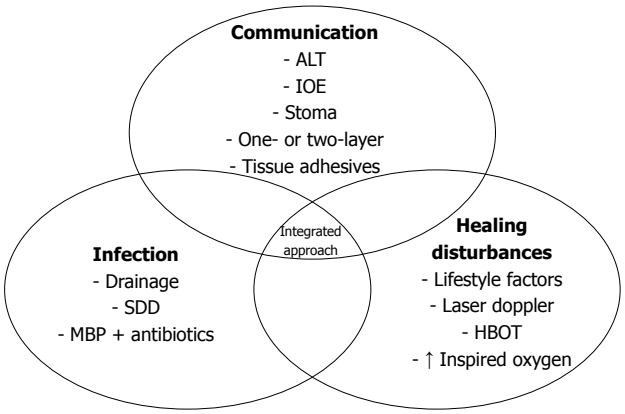

Figure 2 Preventive strategies for colorectal anastomotic leakage with regard to the proposed categorization based on the etiology of colorectal anastomotic leakage (communication, infection and healing disturbances). ALT: Air leaking test; IOE: Intraoperative endoscopy; SDD: Selective decontamination of the digestive tract; MBP: Mechanical bowel preparation; HBOT: Hyperbaric oxygen therapy.

on-going study shows that meta-analysis of previous studies did not find a significant decrease in the rate of CAL in patients who underwent the ALT[28]. This may partly be due to marked variation in ALT methodology. However, we also found a much higher CAL rate in patients who had a leak during the test[28], thus the ALT is still necessary in our daily practice.

Similar to the ALT, intraoperative endoscopy (IOE) is another intraoperative test which, ideally, could allow immediate diagnostic and therapeutic interventions. However, relevant studies on this topic are very limited and show a low level of evidence. Several authors suggest the selective use of IOE in patients during surgery based on their retrospective data. However, there are at least two studies which show that routine IOE does not reduce the CAL rate compared to selective use[29,30]. Since performing IOE requires certain facilities and equipment, it still seems too early to draw conclusions regarding this technique, especially for routine use[31]. Further research on this topic is required.

Another way to prevent communication is to reinforce the anastomosis. One conventional strategy is to perform a second layer anastomosis. This technique has been used for decades, if not centuries, and was once considered the standard technique for colorectal anastomosis. However, studies have shown that the one-layer anastomosis does not result in a higher CAL rate, hence it is as safe as the double-layer technique[32,33]. Due to these non-inferior results, both the one-layer and the double-layer techniques have their own followers and are being used by different surgeons.

Reinforcing an anastomosis with tissue adhesives is used as another strategy and may serve as a sealant and prevent possible microscopic leakage. The most frequently used tissue adhesive in clinical practice is fibrin glue, which is considered to both reinforce the strength of the anastomosis and facilitate wound healing due to its ingredients[34]. However, analysis of the clinical data shows no actual beneficial influence of the intraoperative application of fibrin glue[35].

Our *ex vivo* research demonstrated that fibrin glue, together with many other sealants, were very weak in mechanical tests[36]. Many animal studies have also shown that fibrin glue does not accelerate wound healing[37,38]. Nevertheless, one type of tissue adhesive, cyanoacrylates, has emerged from our series of experiments[39]. This glue is preferred over the other glues in mechanical tests, as it increases the mechanical strength of colorectal anastomosis in both normal and technically insufficient situations[40]. Although animal studies have suggested many promising applications of various tissue adhesives[20,23], clinical data are limited and inconclusive. Further clinical research on this topic is planned by our group.

A temporary stoma is also a technique which prevents communication by diverting the intra-luminal content. Although the effect of preventing CAL with diversion seems unquestionable[41], previous studies on this topic have resulted in different conclusions[42-45]. We should be careful with the unselective use of stomas to prevent CAL as stomas are associated with high complication and comorbidity rates[46]. Therefore, routine diversion with a "temporary" stoma should not

be recommended in regions with sufficient follow-up of the patients.

Prevent infection

Preventing infection is another major area in CAL prevention. One important technique is drainage placement. The purpose of drainage placement seems evident: it helps to eliminate localized toxins and thus prevents infection and its further advancement. Nowadays, drainage placement is omitted in more and more colonic surgeries especially in centers applying the ERAS (Early Recovery After Surgery) program, while in most centers it remains routine practice after anterior rectal resection. However, several contradictory meta-analyses are available regarding the effect of drainage[47-49]. The most recent meta-analysis indicates that a pelvic drain reduces the incidence of extra peritoneal CAL and the rate of re-intervention after anterior rectal resection. These findings are based on the analysis of observational studies. In contrast, the analysis of RCTs did not indicate any benefit of drainage[48].

Another strategy to prevent infection is the application of preoperative selective decontamination of the digestive tract (SDD), which aims to eradicate pathogenic microorganisms with oral antibiotics before elective resection. There is currently one on-going randomized controlled trial, the SELECT trial[50], which is investigating the use of SDD. The results of this trial are expected to further modify the current clinical regimen.

Bowel preparation also follows the concept of preventing infection by eliminating intraluminal pathogens. However, the conventional "mechanical bowel preparation" has been greatly challenged by accumulating evidence which suggests that it may not reduce the risk of CAL, but only substantially delays the return of bowel function[51]. However, evidence for or against the use of oral mechanical bowel preparation is still too weak to change this worldwide clinical practice. Whether bowel preparation should be included into routine preparation for colorectal surgery still requires data from future investigations.

Prevent healing disturbances

Many healing disturbances have been identified as preoperative risk factors of CAL such as diabetes mellitus and smoking. Therefore, a preoperative assessment of the patient's condition is important in the prevention of CAL. Many life-style changes and medical interventions should be arranged before admission. However, the clinical influence of many of these strategies remains unclear and is yet to be determined.

Of course, not all healing disturbances are reversible before surgery. Bowel ischemia contributes to the occurrence of CAL[16,52,53], and therefore intraoperative measurement of the cutting edges may help to detect ischemic edges and may theoretically assist surgeons in the alternative management of the anastomosis (reconstruction or diversion)[54]. However, it is important to note that there is no solid (*i.e.*, high level) evidence supporting such an application. Although observational studies have demonstrated the safety of such a device, it remains unclear whether those detected "ischemic" edges would eventually cause any clinical side effects. Further studies on this topic are necessary before further wide application.

Perioperative tissue oxygen tension measurement could also provide information on anastomotic perfusion[55]. In 1985, it was demonstrated in rabbits that lower tissue oxygen tension was associated with CAL[56]. Therefore, several animal experiments were performed to establish whether Hyperbaric Oxygen Therapy (HBOT) could prevent CAL[57-59]. All studies demonstrated that HBOT increases tissue oxygen tension and improves anastomotic healing. In addition, it is known that high intraoperative inspired oxygen fraction reduces surgical site infections[60,61]. A double-blinded RCT indicated that perioperative supplemental oxygen administration reduced postoperative anastomotic dehiscence after total gastrectomy[62]. The same study group performed a RCT on major rectal cancer surgery and found similar results[63]. With these data, the perioperative application of oxygen therapy seems promising; however, its application is still limited in current clinical practice.

PREDICTION AND EARLY DETECTION

CAL is usually detected between day 5 and day 8 postoperatively, or even later after surgery[64], with more than 50% of cases requiring a reoperation[2,65]. This suggests that with the current strategy many early stages of leakage are not detected until they progress to a severe status. Early diagnosis is necessary as delayed diagnosis of CAL increases postoperative mortality[66]. Figure 3 provides an overview of the methods of prediction and early detection, which have been assessed during the last decades.

In most cases, conventional radiological examinations are still required to confirm the occurrence of CAL. However, decision-making on radiological examinations depends on the surgeon's awareness, which is based on clinical manifestations and laboratory tests. Fever, abdominal pain and prolonged ileus are considered clinical manifestations of CAL but are common after colorectal surgery[67,68]. Based on risk factor analysis and expert opinions, several scoring systems have been developed to predict the individual risk of developing CAL after surgery[69-71]. Dekker *et al*[69] proposed the Colorectal Leakage Score based on the literature and expert opinions. In 2013 den Dulk *et al*[70] suggested the modified DULK score, which evaluated postoperative factors to estimate the risk of CAL. These scores may help the surgeon make an individualized decision, but prospective evaluation of

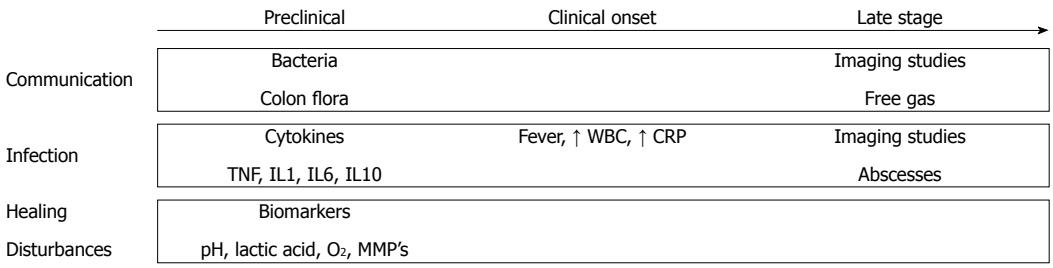

Figure 3 Overview of the methods of prediction and early detection of colorectal anastomotic leakage with regard to the proposed categorization based on the etiology of colorectal anastomotic leakage (communication, infection and healing disturbances). TNF: Tumor necrosis factor; IL: Interleukin; WBC: White blood cell; CRP: C-reactive protein; MMP: Matrix metalloproteinase.

these scores is still limited to date.

Early detection of communication

Imaging studies aim to show whether communication exists between the intra- and extra-luminal compartments of the anastomosis. Routine imaging studies may decrease the interval between diagnosis and treatment of CAL, but are not ideal due to radiation exposure, costs, patient discomfort and false positives because of subclinical CAL[66,72]. In addition, the diagnostic accuracy of imaging tests is still under debate. The sensitivity of CT-scanning for the early detection of CAL varies from 15% to 52%. The main problem for routine use of CT-scanning is the high reported rate of false negatives[73-75]. The other option for radiological evaluation of colorectal anastomoses is contrast radiography. The sensitivity and specificity of this alternative imaging test range from 20% to 52% and from 85% to 87%, respectively, when performed routinely at postoperative day 7 or 8[76,77]. When contrast radiography is performed in patients with clinical symptoms, the diagnostic accuracy is reported to be higher, with a sensitivity of 68% and a specificity of 94%[73]. Nevertheless, we should be aware that the interval between operation and the examination is often more than a week, indicating that this technique may not be adequate in detecting CAL at an early stage, but only when leakage has already progressed to a severe state in which abscesses or free gas are already present and indicated by imaging studies.

Recent studies focus on innovative strategies to detect CAL as routine radiological examinations are not preferred because leakage is detected at a relatively late stage. An early screening tool for CAL could be the detection of colon flora in drain fluid. The presence of colon flora in drain fluid is suggestive of communication between intra- and extra-luminal compartments and causes infection at the anastomotic site in patients with leakage[2]. Although promising, there are few studies which have considered the predictive value of bacterial measurement in drain fluid. Fouda *et al*[78] evaluated intraperitoneal bacterial colonization using cultures during the early postoperative period after rectal surgery. *Escherichia coli*, Bacteroides and Pseudomonas showed significant differences between leaking and non-leaking patients at postoperative day 1, 3 and 5. These results indicate that this method may decrease the period to diagnosis of CAL. However, it takes at least 48 hours before bacteria can be identified on quantitate cultures, resulting in an inevitable delay in diagnosis. Therefore, Komen *et al*[79] proposed the use of RT-PCR techniques for the detection of bacteria in drain fluid. This technique is much faster, more sensitive and less susceptible to contamination than culture. It achieved a negative predictive value of 98.7%, although its positive predictive value was unsatisfactory (31.6%).

Early detection of infection

Leukocyte count and serum C-reactive protein (CRP) levels are often abnormal after surgery both in CAL patients and in a substantial number of patients with uncomplicated recovery. Therefore, these parameters have a limited predictive value for CAL[67,80]. In 2014, a meta-analysis by Singh *et al*[81] was published which assessed the predictive value of serum CRP levels for CAL. Rather than determining the positive predictive value, this article reported a negative predictive value of 97% for CRP on postoperative day 3-5, while the corresponding positive predictive value for leakage ranged between 21% and 23%.

In addition to white blood cell count and CRP levels, other innovative inflammatory biomarkers have also been tested in several studies for the early detection of CAL. Inflammatory cytokines such as TNF-a, IL-1b, and IL-6 have been evaluated in both peritoneal drain fluid and blood samples. Cini *et al*[82] performed a meta-analysis and found that cytokine levels in drain fluid were significantly higher in CAL cases. However, Ellebæk *et al*[83] reported that serum levels of inflammatory cytokines were the same in patients with CAL and in those with normal recovery. This is because the onset of CAL is a progressive process. A localized response at the site of the anastomosis occurs before systemic changes such as fever, leukocytosis and septic symptoms become manifest[84]. Therefore, monitoring changes in cytokine levels in drain fluid could contribute to the early detection of CAL[85], while systematic changes remain latent until CAL is at an advanced stage[86]. The data from these studies seem promising; however, the main problem with the available literature

is that these reports provide a low level of evidence due to low sample sizes, poor patient selection and lack of standardization[78,87-91]. Further examination of these parameters may be an interesting topic for future studies.

Early detection of healing disturbances

As many metabolic biomarkers represent healing disturbances, the detection of metabolic parameters may be another strategy for the early detection of CAL. However, clinical data on this topic are very limited, mainly due to a lack of proper sensors[18]. Daams *et al*[92] showed promising results using the minimally invasive method of intraperitoneal microdialysis. This technique enabled measurement of real-time local ischemia and changes in metabolism by establishing dialysate levels of lactate, pyruvate, glucose and glycerol[93-95]. Due to a lack of clinical data, how to correctly interpret these metabolic data and associate them with anastomotic healing remains difficult and requires further investigation[96,97].

INTERVENTION

Once leakage has occurred, an effective intervention should be undertaken to control morbidity and mortality. The ultimate goal of prediction or early detection of CAL is to initiate timely treatment to improve patient outcome. The type of intervention strongly depends on the severity of CAL, which as discussed above, is hard to determine and therefore the choice of intervention for a suspicious leakage is quite complex with very limited evidence available at present[2].

Despite individual experience from surgeons, the best knowledge regarding intervention in CAL came from a Delphi analysis, which used an expert panel and aimed to emphasize consensus[98] and to construct evidence-based guidelines[99]. Phitayakorn *et al*[100] used this technique to develop a treatment algorithm for CAL.

Interventions for CAL can be divided into two main groups: treatment of infection and treatment of communication. Interventions which prevent communication also contribute to infection control, therefore most interventions for CAL require an integrated approach.

Administration of antibiotics is often the first intervention when CAL is suspected. Antibiotics are usually modified after the results of the susceptibility test are obtained when drainage or blood samples are cultured. A retrospective study showed that both surgical and non-surgical interventions based on the presentation of CAL are both effective and safe[101]. There are several surgical intervention options: drainage, repair of the anastomosis, deviating ileostomy or permanent colostomy. It is known that a stoma after colorectal surgery moderates quality of life. Moreover, half of patients who undergo the formation of a stoma due to CAL are left with a permanent stoma[102]. Given that routine construction of a stoma for CAL repair should not be recommended, alternative surgical strategies should be discussed and considered before reoperation[103].

If surgical re-intervention is indicated, and the surgeon decides to construct a stoma, the choice between diversion of the anastomosis with a loop ileostomy and resection of the anastomosis with end colostomy should be made. A questionnaire completed by members of the Dutch Society for Gastrointestinal Surgery showed that Dutch colorectal surgeons prefer to preserve the anastomosis in young non-septic patients, whereas the anastomosis is broken down and a colostomy is constructed in older patients or in those with abdominal sepsis[104]. Despite the surgeon's experience, this choice strongly depends on the severity of leakage and comorbidities in the patient[105]. Some data suggest that diversion with loop ileostomy is safe and is associated with less mortality and morbidity if no sepsis or fecal contamination is present[106,107], but no solid evidence or consensus is available in this regard.

Most re-interventions were initiated with an open approach until recently when two retrospective cohort studies showed that laparoscopic re-intervention for CAL was safe and feasible[108,109]. With more and more surgeons experienced in the laparoscopic approach, we may expect laparoscopy as the first choice for re-interventions in the future.

CONCLUSION

CAL remains the most dangerous complication after colorectal surgery. Surgeons still have to deal with this critical issue mainly based on their experience and limited knowledge from the literature. In this review, we proposed an integrated etiology of CAL, consisting of three major parts including communication, infection, and healing disturbances. Based on the etiology, we categorized the currently available strategies into at least one of these major factors. This simplified categorization may contribute to our integrated understanding of CAL. All three aspects should be taken into consideration during clinical practice regarding prevention, prediction, early detection and intervention of CAL, which we believe will eventually facilitate an integrated approach for CAL and result in better patient outcome.

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