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**Integrated approach to colorectal anastomotic leakage; communication, infection and healing disturbances**

Sparreboom CL *et al*. Integrated approach to colorectal anastomotic leakage

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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 been reduced. In this review, we summarized available strategies regarding prevention, prediction and intervention of CAL and categorized 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 on 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 patients’ outcomes.

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

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**Core tip:** Colorectal anastomotic leakage (CAL) remains the most dangerous complication after colorectal surgery. In this review, we proposed an integrated approach of CAL, consisting of three major parts including 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 in the end better patients’ outcomes.

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**Introduction**

Colorectal anastomotic leakage (CAL) still remains a frequent and dangerous complication after gastrointestinal surgery, occurring in 4%-33% 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 and 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 recoveries[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 explored techniques targeting on prevention, detection and intervention of CAL, but little attention has been paid into a systematic categorization of these strategies. To this end, we aim to provide surgeons an integrated understanding of those 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 etiology of CAL in detail. In many previous studies, CAL is attributed to technical failure or ischemia[15,16], but neither of them seems to explain the whole mechanism[17]. In the end, this emphasizes the need for an integrated approach regarding etiology of CAL.

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

Communication stands for 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 because of two reasons. First, based on our observations and the previous studies, evidence regarding these three aspects was always observed in the leaking cases 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 found as the main course in CAL cases, which may also cause the other two since 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 the previous literature, surgeons and researchers often categorize these strategies based on the time of application (*e.g.,* preoperative, intraoperative and postoperative)[26]. In addition to that, we divide 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 used most frequently as an intraoperative test in colorectal surgery to identify technically failed anastomosis, which may cause direct communication between intra- and extra luminal compartments. The rate of this intraoperative test varies greatly among studies evaluating ALT[27]. Surprisingly, our on-going study shows that meta-analysis of previous studies did not find a significantly decrease of CAL rate in the patients underwent ALT (unpublished data). This may partly be due to great variation in ALT methodology. However, we also found a much higher CAL rate in the patients who had a leak during the test (unpublished data), so ALT remains necessary in our daily practice.

Similar to ALT, intraoperative endoscopy (IOE) is another intraoperative test which, ideally, could provide immediate diagnostic and therapeutic interventions. However, relevant studies on this topic are very limited and of low level of evidence. Several authors suggest a selective use of IOE in suspicious 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[28,29]. Since performing IOE requires certain facilities and equipment, it still seems too early to draw conclusions of this technique, especially for routine use[30]. 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 as the standard technique of colorectal anastomosis. However, studies have shown that the one-layer anastomosis does not result in higher CAL rate, hence is as safe as the double-layer ones[31,32]. Because of those non-inferior results, both the one-layer technique and the double-layer one have their own followers and are being used by different surgeons.

Reinforcing an anastomosis with tissue adhesives has been implemented 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 anastomotic strength and facilitate wound healing by its ingredients[33]. However, analysis of the clinical data shows no actual beneficial influence of intraoperative application of fibrin glue[34].

Our ex-vivo research demonstrates that fibrin glue, together with many other sealants, are very weak in the mechanical tests[35]. Many animal studies also have shown that fibrin glue does not accelerate wound healing[36,37]. Nevertheless, one type of tissue adhesive, cyanoacrylates, has emerged from our series of experiments[38]. This glue is preferred over the other glues in mechanical tests, increasing the mechanical strength of colorectal anastomosis in both normal and technical insufficient situations[39]. Although animal studies have suggested many promising applications of varying tissue adhesives[20,23], clinical data on this regard remain limited and inconclusive. Further clinical research on this topic has been planned in our group.

A temporary stoma is also a technique that prevents communication by diverting the intra-luminal content. Although the effect of preventing CAL with diversion seems unquestionable[40], previous studies on this topic still result in different conclusions[41-44]. We should be careful with the unselective use of stomas to prevent CAL since stomas are associated with high complication and comorbidity rates[45]. 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 branch 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 advancing. Nowadays, drainage placement has been omitted in more and more colonic surgeries especially in the centers applying the ERAS (Early Recovery After Surgery) program, while in most centers it remains routine practice after anterior rectal resection. However, several contradicting meta-analysis are available regarding the effect of drainage[46-48]. The most recent meta-analysis indicates that 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 the RCTs did not indicate any benefit of drainage[47].

Another strategy to prevent infection is application of preoperative selective decontamination of the digestive tract (SDD), which aims to eradicate pathogenic microorganisms with oral antibiotics before elective resection. At this moment there is one on-going randomized controlled trial, the SELECT trial[49], which investigates the use of SDD. Its results are expected for further modification of the current clinical regimen.

Bowel preparation also follows the concept of preventing infection by cleaning the intraluminal pathogens. However, the conventional “mechanical bowel preparation” has been greatly challenged by the accumulating evidence that it may not reduce the CAL risk but only substantially delaying the return of bowel function[50]. However, evidence either for or against the use of oral mechanical bowel preparation is still too weak to revolute the worldwide clinical practice. Whether to include it into routine preparation for colorectal surgery still requires further knowledge from future investigations.

***Prevent healing disturbances***

Many healing disturbances are identified as pre-operative risk factors of CAL such as Diabetes Mellitus and smoking. Therefore, a proper preoperative preparation of the patient’s condition is important in prevention of CAL. Many life-style changes and medical interventions shall 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 occurrence of CAL[16,51,52], and therefore intraoperative measurement of the cutting edges may help to detect those ischemic edges and may theoretically assist surgeons for alternative management of the anastomosis (reconstruction or diversion)[53]. However, it is important to address that there is no solid (*i.e.*, high level) evidence supporting such application. Although observational studies have demonstrated the safety of such device, it remains unclear whether those detected “ischemic” edges would eventually cause any clinical side events. Further studies on this topic remain necessary before further wide application.

Perioperative tissue oxygen tension measurement could also provide information about anastomotic perfusion[54]. In 1985 it was already demonstrated in rabbits that lower tissue oxygen tension is associated with CAL[55]. Therefore several animal experiments were performed to establish whether Hyperbaric Oxygen Therapy (HBOT) could prevent CAL[56-58]. All studies demonstrated that HBOT increases tissue oxygen tension and improves anastomotic healing. Besides, it is known that high intraoperative inspired oxygen fraction reduce surgical site infections[59,60]. A double-blinded RCT indicates that perioperative supplemental oxygen administration reduces postoperative anastomotic dehiscence after total gastrectomy[61]. The same study group performed a RCT regarding major rectal cancer surgery and found similar results[62]. With these data, perioperative application of oxygen therapy seems promising, and its application nonetheless is still limited in the current clinical practice.

**Prediction and early detection**

CAL has usually been detected between day 5 and day 8, or even later after surgery[63], with more than 50% of the cases requiring an reoperation[2,64]. This suggests that with current strategy many early stages of leakage cases are not detected until progressing to a severe status. Earlier diagnosis should be strived for since delay in diagnosis of CAL increases postoperative mortality[65]. Figure 3 provides an overview of methods of prediction and early detection, which have been explored 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 surgeon’s awareness, which is based on clinical manifestations and laboratory tests. Fever, abdominal pain and prolonged ileus are considered as clinical manifestations of CAL and are common after colorectal surgery[66,67]. Based on risk factor analysis and expert opinions, several scoring systems have been developed to predict the individual risk of developing CAL after surgery[68-70]. Dekker *et al*[68] proposed the Colorectal Leakage Score (CLS) based on literature and expert opinions. In 2013 den Dulk *et al*[69] suggested the modified DULK score, which evaluated postoperative factors to estimate the risk of CAL. Theses scores may help the surgeon make an individualized decision, but prospective evaluation of these scores is still limited to date.

***Early detection of communication***

Imaging studies aim to show whether communication exist between the intra- and extra luminal compartments of the anastomosis. Routine imaging studies might 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[65,71]. Besides, the diagnostic accuracy of imaging tests is still under debate. The sensitivity of CT-scan for the early detection of CAL varies from 15% to 52%. The main problem for routinely use of CT-scan are the high reported rates of false negatives[72-74]. The other option for radiological evaluation of colorectal anastomoses consists of contrast radiography. The sensitivity and specificity for this alternative imaging test vary between 20 to 52% and 85 to 87% respectively when performed routinely at postoperative day 7 or 8[75,76]. When contrast radiography is performed in case of clinical symptoms the diagnostic accuracy is reported to be higher, with a sensitivity of 68% and a specificity of 94%[72]. Nevertheless, we should be aware of the fact that the interval between operation and the examination is often more than a week, implying that this technique may not be adequate in detecting CAL in an early stage but only when leakage is already progressed to a severe state in which abscesses or free gas are already present and indicated with imaging studies.

Recent studies focus on innovative strategies techniques to detect CAL since routine radiological examinations are not preferred because this technique detects leakage in a relatively late stage. An early screening tool for CAL could be detection of bacteria of the colon flora in drain fluid. Presence of colon flora in drain fluid is suggestive for communication between intra- and extra luminal compartments and causes infection at the anastomotic site in case of leakage[2]. Although promising, there are not many studies considering the predictive value of bacteria measurement in drain fluid. Fouda *et al*[77] evaluated intraperitoneal bacterial colonization by cultures during the early postoperative period after rectal surgery. *E. 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 might decrease the period to diagnosis of CAL. Nevertheless, it takes at least 48 hours before bacteria can be identified on quantitate cultures, which is an inevitable delay. Therefore komen *et al*[78] proposed to use 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 predicted value of 98.7%, although its positive predictive value seems 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 substantial uncomplicated recoveries. Therefore, these parameters do have a limited predictive value for CAL[66,79]. In 2014 a meta-analysis by Singh *et al*[80] was published which assesses the predictive value for CAL of serum CRP levels. Rather than determining the positive predictive value, this article reports a negative predictive value of 97% of CRP on day 3-5 postoperatively, while the corresponding positive predictive value for leakage ranges between 21% and 23%.

In addition to white blood cell count and CRP levels, other innovative inflammatory biomarkers are also tested in several studies for 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. performed a meta-analysis and found that cytokine levels in drain fluid are significantly higher in CAL cases[81]. However, Ellebaek *et al*[82] reported that serum levels of inflammatory cytokines remain the same between the CAL cases and the normal recoveries. 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[83]. Therefore monitoring changes of cytokine levels in drain fluid could contribute to early detection of CAL[84], while systematic changes remain latent until CAL advances to a late stage[85]. The data from these studies seem promising, however, the main problem with available literature is that they provide low level of evidence due to low samples sizes, poor patient selection and lack of standardization[77,86-90]. Further exploration of these parameters may be one interesting topic for future studies.

***Early detection of healing disturbances***

Detection of metabolic parameters might be another strategy for early detection of CAL because many metabolic biomarkers represent healing disturbances. However, clinical data on this topic is very limited so far, mainly due to a lacking of proper sensors[18] F. Daams *et al*[91] showed promising results using a minimally invasive method of intraperitoneal microdialysis. This technique enables measuring real-time local ischemia and changes in metabolism by establishing dialysate levels of lactate, pyruvate, glucose and glycerol[92-94]. Due to lack of clinical data, how to properly interpret these metabolic data and associate them with anastomotic healing remains difficult and still requires further investigations[95,96].

**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 timely initiate treatment to improve patients’ outcomes. 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 this moment[2].

Despite individual experience from surgeons, the best knowledge regarding intervention of CAL came from a Delphi analysis, which uses an expert panel and aims to emphasize consensus[97] and to construct evidence-based guidelines[98]. Phitayakorn et al. used this technique to develop a treatment algorithm for CAL[99].

Interventions of CAL could be divided in to two main groups: treatment of infection and treatment of communication. Interventions that prevent communication also contribute to the infection control and therefore most interventions for CAL do already acknowledge the need for an integrated approach.

 Administration of antibiotics is often the first intervention when CAL is suspected. Antibiotics are usually modified after the susceptibility test by culturing drainage or blood samples. A retrospective study assesses that both surgical and non-surgical interventions based on the presentation for CAL are both effective and safe[100]. 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 the patients who underwent formation of a stoma due to leakage have been left with a permanent stoma[101]. Given that, routine construction a stoma for CAL repairing should not be recommended and alternative surgical strategies should be discussed and considered before reoperation[102].

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 undertaken amongst members of the Dutch Society for Gastrointestinal Surgery shows that Dutch colorectal surgeons prefer preserving the anastomosis in non-septic young patients whereas the anastomosis is broken down and a colostomy was constructed in older patients or abdominal sepsis[103]. Despite the surgeon’s experience, this choice strongly depends on severity of leakage and comorbidities of the patient[104]. 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[105,106], but no solid evidence or consensus is available in this regard.

Most re-interventions have been initiated with an open approach until recently two retrospective cohort studies show that laparoscopic re-intervention for CAL is safe and feasible[107,108]. With more and more surgeons experienced in laparoscopic approach, we may expect laparoscopy as a first choice for the re-intervention 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 the 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 categorize the currently available strategies into at least one of those major factors. This simplified categorization may contribute to our integrated understanding of CAL. All these three aspects should be taken into consideration during our clinical practice regarding prevention, prediction, early detection and intervention of CAL, which we believe will eventually facilitate an integrated approach to CAL and in the end better patients’ outcomes.

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



**Figure 2 Preventive strategies of 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.



**Figure 3 Overview of 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.