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Prediction and Early Identification of Anastomotic Leaks after Colorectal Surgery

Gabriel Popescu[1], Șerban Bancu[1,2], Daniela Sala[1,2], Radu Mircea Neagoe[1,2]* and Mircea Mureșan[1,2]

[1]*Department of Surgery, 2nd Surgical Unit, Emergency County Hospital, Târgu Mureș, Romania*
[2]*University of Medicine and Pharmacy, Târgu Mureș, Romania*

Abstract

Anastomotic leaks (AL) still represent a major possibly life-threatening complication after colorectal surgery. The clinical presentation varies from mild symptoms to peritonitis and sepsis, which toughens the early diagnosis even for experienced surgeons. Numerous risk factors have been identified in the development of AL. The presence of bacterial strains such as *Pseudomonas aeruginosa* or *Enterococcus faecalis* are associated with higher AL rates, thus antibiotic prophylaxis seems to reduce complications. Male gender, advanced age, higher ASA fitness score, malnutrition and personal history of radiotherapy, diabetes mellitus and chronic kidney disease also lead to higher AL rates. The localization of the tumor also represents an important risk factor, as distal tumors have been identified as a predictor for AL. No differences have been found between open versus laparoscopic surgery as well as hand-sewn versus stapled anastomoses. The timing of the operation and the experience of the operating teams also affects both short and long-term. Early identification of AL is the key to reduction of mortality rates, thus scoring systems such as the Dutch Leakage Score have been developed and validated to aid surgeons for timely diagnosis. Modern imaging techniques and laboratory biomarkers further shorten the delay to a proper and early diagnosis. Computed tomography can identify even subclinical AL, leading to improved outcomes. Laboratory biomarkers such as C-reactive protein and procalcitonin are validated by large randomized studies as useful tools for exclusion of AL, possessing high negative predictive values.

Keywords

Colorectal surgery; Colorectal resections; Colorectal anastomosis; Anastomotic leak; Inflammatory response; C-reactive protein; Procalcitonin

Introduction

Regardless of the modern surgical techniques developed over the last decades anastomotic leaks (AL) still represent one of the most important and dreaded complications in colorectal surgery. It is associated with high morbidity and mortality rates, frequent need of repeated surgical intervention and readmission as well as with prolonged hospitalization and decreased quality of life for the patient [1,2]. Furthermore, AL has been associated with worse oncological results due to the interruption or deferment of the adjuvant chemotherapeutic treatment [3]. These complications generate considerable costs for any healthcare system [4]. The overall incidence of AL after colorectal surgery is reported around 1.6%-16% and widely varies between hospitals and surgery departments depending on many factors linked both to the operator and the comorbidities of the patient [5]. The AL linked mortality ranges between 5%-28% and some authors suggest that the 30-day mortality rate is associated with the length of hospitalization [6-8]. Prediction and early recognition of AL is a challenging task for every surgeon due to the multitude of clinical presentations, which are often indistinguishable from the symptoms caused by the physiological inflammatory response after colorectal surgical procedures [9]. In most cases, these signs and symptoms may vary from mild abdominal pain and fever to ileus, fulminant peritonitis, sepsis and death [10]. Anastomotic leaks usually appear between day 5 to 8 after the surgery, but in some cases it may show a delayed presentation as late as the 13th postoperative day [11]. It has been demonstrated that, regardless of the experience and training, the clinical assessment of the surgeon alone is inadequate in identifying patients at high risk for AL and for early diagnosis of leakages [12]. Multiple diagnostic methods have been proposed for early identification of AL, but no consensus exists over the correct guidance in the management of this major postoperative complication. Laboratory biomarkers such as C-reactive protein (CRP) and white blood cell count, as well as radiological examinations may come in the aid of surgeons for a prompt identification of this life-threatening condition [13,14].

The aim of this review is to provide a comprehensive summary on the modern management of anastomotic leaks in colorectal surgery.

Clasification and risk factors

Numerous studies have investigated the causes of anastomotic leaks in the past decade in order to prevent and efficiently treat this perioperative complication that is associated with high risk of mortality. None of the authors succeeded in elaborating a standardized definition of the AL that would be generally accepted by the surgical community [15]. According to the International Multispecialty Anastomotic Leak Global Improvement Exchange (IMAGInE) group, AL is defined as a defect of continuity localized at the surgical site of the anastomosis, which creates a communication between intraluminal and extraluminal compartments. This definition is adapted from the previously validated proposal of the International Study Group of Rectal Cancer. Respecting this classification, AL can be classified into three grades. Grade A with minimal clinical impact, which does not require an active therapeutic action, grade B, which does not require surgical re-intervention, but

***Corresponding author:** Radu Neagoe, MD, PhD, Associate Professor of Surgery, Department of Surgery, 2nd Surgical Unit, Emergency County Hospital Târgu Mureș, Str. Gh. Marinescu No 50, Târgu Mureș, Romania, Tel: +40065212111/273;; E-mail: neagoerm@gmail.com

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therapeutic measures must be initiated and grade C, which requires repeated surgical intervention [16,17].

Pathophysiology

The course of the natural healing process of anastomotic wounds occurs in four phases, and it extends to as long as one year after the surgical intervention. The first stage, the hemostasis phase, occurs within seconds after the injury and involves activation of platelets and the coagulation cascade. The second, or inflammatory phase, is directed by the immune system as a response to the injury and it involves neutrophils, lymphocytes and macrophages in order to eliminate the microorganisms and debris that may contaminate the wound. This phase occurs in the first 10 days after the injury, and is followed by the proliferative phase (between days 5-21) which results in re-epithelization of the injury site, being mediated by growth factors that regulate fibroblasts and endothelial cell proliferation. The final stage of wound healing extends from day 21, up to one year, and it results in complete restoration of the injury site by stromal cell with collagen formation [18,19]. Each phase of the healing process may be affected by a multitude of local and systemic factors.

Etiology of AL

Bacteriological factors: The abundant bacterial colonization plays an important role in the physiological function of the intestinal wall, contributing to nutrient absorption and to a normal immune activity [20]. Nevertheless, some microbial strains are considered possible etiological factors in the appearance of ALs. Early preclinical studies have suggested a positive association between inoculation with *Pseudomonas* strains and development of AL in rats. Schardey et al. had orally infected rats with *Pseudomonas aeruginosa* strains in the first postoperative day after total gastrectomy, followed by esophagoduodenostomy and compared the results to a control group which had received oral antibiotic therapy from the seventh postoperative day. A significantly higher rate of anastomotic insufficiency was noticed in rats inoculated with *P. aeruginosa* (95% vs. 6%, $p<0.001$) compared to controls. Furthermore, other complications such as peritonitis ($p<0.05$), abscesses ($p<0.05$) and mortality ($p<0.05$) were significantly reduced, in the decontaminated group, raising the question for the role of bacterial strains in the appearance of AL and the possible protective effect of antibiotics for prevention [21]. These results were confirmed in a randomized double-blind multicenter clinical trial, conducted by the same authors, in which 260 patients with gastrectomy were included, and placebo administration was compared to perioperative administration of polymyxin, tobramycin, vancomycin and amphotericin B. The trial resulted in lower morality rates (4.9% vs. 10.6% $p=0.1$) and significantly reduced rates of AL of esophagojejunostomy in patients receiving antimicrobial treatment (2.9% vs. 10.6%, $p<0.04$) [22]. Further studies have investigated the role of bacterial activity in the pathogenesis of AL by production of collagenolytic proteins, which locally lead to disintegration of the extracellular matrix in anastomotic wound structures [23]. In a recent study, Shogan et al. demonstrated the role of microbial infection with *Enterococcus faecalis* in the appearance of intestinal AL, due to their capacity of collagen degradation and matrix metalloprotease (MMP) activation in rat models. In addition, intravenous administration of recommended standard antibiotic therapy after colorectal surgery did not eliminate *E. faecalis* from the anastomotic tissue, but application of topical antibiotics which targeted the eradication of *E. faecalis* prevented AL [24]. In a meta-analysis, Oines et al. analyzed the role of MMP inhibitors in preventing AL after colorectal surgery. The authors concluded that MMP inhibitors improved anastomotic strength in animal models, but no significant reduction of AL was noted in the only human study which included 103 patients with colorectal surgery (11.7% vs. 9.7%) [25].

General factors for anastomotic leakage: Multiple studies have investigated the patient-related components that may represent risk factors for the appearance of AL. Male gender has been identified as risk factor for AL regardless of the type of colorectal surgery [26,27]. This might be explained by the anatomic differences between male (narrower diameters) and female pelvis and role of androgenic hormones on the microcirculation of the intestines [28,29].

Advanced age has also been associated with greater risk for AL. In a large study which included 1391 patients with rectal resection, Jung et al. identified the age over 60 years as an independent risk factor for AL (hazard ratio 2.32) [30].

The American Society of Anesthesiologists (ASA) fitness grade of patients has been greatly correlated with the risk of developing AL. In a study that analyzed 811 colorectal anastomoses, Buchs et al. stated that a III or greater ASA score is associated with 2.5-fold risk for AL [31]. In a large national registry study that included over 15,000 patients, Bakker et al. confirmed higher ASA score as an independent risk factor for AL [32].

The nutritional status of the patient also plays a role in the development of AL, as appropriate nutrient and electrolyte levels are essential for collagen synthesis and normal immune activity, thus malnutrition may lead to impaired wound healing [33]. Numerous trials have demonstrated that preoperative weight loss and malnutrition disorders are associated with higher AL rates [34,35]. Anemia or low albumin levels (<3.5 g/dl) may also contribute the anastomotic dehiscence through the same pathophysiological mechanism mentioned above [36,37].

The medical history of the patient, including comorbidities and behavioral factors contribute to the risk of developing AL. Previous radiotherapy can represent an important predictor of AL due to alteration of the vascular bed and impaired fibroblast and growth factor activity, leading to increased fibrosis [38,39]. In a meta-analysis including an impressive number of patients (n=110,272), Pommergaard et al. have identified preoperative radiotherapy as an independent risk factor for development of AL (OR 1.65, 95% CI: 1.06-2.56, $p=0.03$) [40]. Diabetes mellitus impairs wound healing because of its vascular and metabolic disturbances. Volk et al. have identified diabetes as an important predictor for AL (OR 4.25, 95% CI: 0.973-18.630, $p=0.05$) [41]. However, the role of diabetes in AL is somewhat debated as other authors suggest that there is no significant increase of AL rate in diabetic patients [42]. Patients with history of renal disease are also at higher risk for AL [43]. Numerous studies have investigated the risk factors associated with patient behavior, in which smoking, obesity and excessive alcohol consumption have been identified as relevant risk factors for AL [44-46].

Surgery related factors for anastomotic leakage: Current literature data highlights that localization of the anastomosis can predict the prevalence of AL, as the rate of AL greatly varies between the intestinal segments [47]. In a recent systematic review, McDermott et al. have shown that the rate of AL for colorectal and coloanal anastomoses can be as high as 5-19% compared to ileocolic (1-4%), colocolic (2-3%) and ileorectal (3-7%) anastomoses [48]. The distance from the anal verge was found to be an important predictor for AL. In a study which included 475 patients with rectal tumor resection, Tortorelli et al. reported a significantly higher rate of AL if the tumor was located at <6 cm from the anal verge (13.7 vs. 6.6%, $p=0.011$) [49]. Akiyoshi et al. also reported that middle/lower rectal cancer is an independent predictor for AL (OR 9.44, 95% CI: 1.172-76.133, $p=0.03$) [50]. Cong et al. published the results from 738 patients who underwent anterior resection for rectal cancer and stated that AL rate for low rectal cancer resection located at less than 7cm from the anal verge was significantly higher compared to high rectal cancers [51].

The use of mechanical suture techniques has also been intensely investigated in a large number of randomized controlled trials. In a recent meta-analysis that reviewed 7 studies, Naumann et al. compared stapled versus hand-sewn anastomoses in the setting of emergency laparotomy, and found no differences between the two techniques in respect to AL [52]. In a Cochrane review which analyzed 9 trials, on a total of 1233 patients, there was no evidence in favor of stapled over hand-sewn procedures, regardless of the tumor localization [53]. New mechanical techniques have emerged, such as compression the anastomosis ring device. In a review article, Zbar et at. reported similar AL rates compared to stapler techniques, but further studies are required to prove the safety and efficacy of this technique [54].

The comparison of the efficiency of laparoscopic versus open surgery has been the subject of numerous studies and similar results were obtained for both techniques in respect of AL rates [55,56]. In a Cochrane review on 14 studies, which included 3528 patients with rectal cancer, found no differences between the two techniques in terms of AL rates [57]. Robotic surgery may represent an alternative to colorectal surgery, but due to high costs and yet controversial results, it is not a widespread technique. In a review article, Kim et al. reported no significant differences between robotic and laparoscopic rectum resection in regards to AL, with slightly lower rates in case of robotic interventions [58]. In a recent study that included 1029 patients, Cho et al. also found similar AL rates in laparoscopic versus robotic resection (10.8% for laparoscopic vs. 10.4% for robotic resection, $p=1$) [59].

Timing of the surgical intervention has a major impact on both long and short term outcomes, because of frequent complications. Emergency surgery is considered a major risk factor for developing AL. In a multivariate analysis, Bakker et al. identified emergency surgery as an independent predictor of AL (OR 1.33, 95% CI: 1.11-1.59, $p=0.002$) [32].

The experience of the operating team in colorectal surgery may also play a role in the development of AL, but the literature data is ambiguous. Cong et al. related significantly lower AL rates when the operation was performed by colorectal surgeons compared to non-specialized operators (3.9% vs. 11.3%, $p=0.03$) [51]. Some authors suggest that AL rates are lower in the case of high-volume surgeons, but other studies found no significant differences in terms of AL when the surgeons' experience was analyzed [60,61].

Diagnosis of anastomotic leaks

An accurate diagnosis of AL is challenging due to its diverse clinical presentation and the multitude of symptoms and studies have demonstrated that even experienced surgeons have low sensitivity and specificity in predicting AL [12,62]. In early stages of AL, patients can be completely asymptomatic, while in many cases the first sign of AL can be represented by peritonitis and septic shock. Sutton et al. reported the results of a study on the clinical presentation of AL, and found that an astonishing 69% of patients with AL were misdiagnosed in the first stage as they presented cardiac symptoms, which led to a delayed surgical diagnosis [10,63]. A deferred AL diagnosis is associated with significantly higher mortality and morbidity rates [64].

Risk scores for early diagnosis of AL: Several scoring systems have been developed for early prediction and diagnosis of AL. Lie et al. developed a scoring system for prediction of AL after anterior resection for rectal cancer. The system is based on the analysis of the risk factors of 1060 patients and identified a high (4-5 score), intermediate (2-3) and low risk (0-1) population that was associated with 16.1%, 8% and 1.9% AL rate ($p<0.001$) [65]. Another scoring system that proposes to predict AL after left sided colon surgery is the colon leakage score (CLS). It scores patient and operation related risk factors and defines low and high risk anastomoses [66]. Both scoring systems need further validation.

A widespread standardized and validated scoring system for early identification of AL is represented by the Dutch Leakage Score (DULK) and the modified DULK score, which is based on clinical (patient condition, abdominal pain, respiratory rate) and laboratory (CRP level) assessment, with a high sensitivity (97%) and negative predictive value (99.5%) and an overall sensitivity of 57% [67,68]. The reliability of this scoring system has been further validated by recent studies and its implementation and the routine clinical practice has been proposed for timely diagnosis of AL [69].

Imaging and laboratory biomarkers for early diagnosis of AL: Imaging studies may be able to identify even subclinical ALs, thus shortening the delay to the diagnosis and improving short- and long term outcomes. Computed tomography (CT) demonstrated variable sensitivity and specificity in identification of AL, but it is one of the most widely used imaging methods [70]. The efficiency of this technique can be improved by administration of intraluminal contrast material and water soluble enema (WSE). Some studies even suggest that the combined use of these methods can enhance sensitivity to 100% in identification of AL in selected cases [71]. In a systematic review, Daams et al. proved the accuracy of CT in detection of colorectal AL, and concluded that CT scans should represent the methods of choice for diagnosis of AL in colorectal surgery [72].

Role of biomarkers: Along the clinical observation, it is important to distinguish the physiological response following colorectal surgery and the signs of a major inflammatory event, which may forecast an important complication such as AL or sepsis [73]. CRP is a non-specific acute phase protein than can identify AL before the onset of symptoms and changes in other laboratory parameters such as white blood cell count can be used as markers for the systemic inflammatory response that can precede an AL [74,75]. A great number of studies have investigated the role of CRP in early identification of AL. In meta-analysis that investigated 7 clinical studies, including 2483 patients, Singh et al. concluded that determination of CRP in day 3, 4 and 5 after surgery, with cut-off values of 172 mg/l, 124 mg/l and 144 mg/l, possesses a negative predictive value (NPV) of 97% in excluding ALs [76]. Furthermore, the combination of CRP and procalcitonin, assessed in day 5 following surgery, with a cut-off value of 0.31 ng/ml, has been identified as a reliable predictor for AL with a 100% sensitivity, 72% specificity, 100% NPV, 17% positive predictive value [77]. These findings were confirmed by the recent PREDICS study, which found that procalcitonin had a NPV of 96.9% on postoperative day 3 and 98.3% on postoperative day 5 (cut-off value 2.3 ng/ml), with a specificity of 91.7% and 93% respectively. CRP also exhibited good NPV 96.4% on postoperative day 3 (cut-off value 16.9 mg/ml) and 98.4% on postoperative day 5 (cut-off value 12.5 ng/ml). The combination of CRP and procalcitonin determination further improved diagnosis of AL (AUC 0.842 on postoperative day 3 and 0.901 on postoperative day 5 [78]. The usefulness of other biomarkers such as interleukin-1, -6, -10, cytokines, tumor necrosis factor alpha and various metalloproteinases have also been investigated, but these are still in the experimental phase and further studies are needed [79].

Conclusion

Despite the technical and technological advancements, anastomotic leaks are still a relatively frequent complication after colorectal surgery, with potentially lethal consequences. Prevention and early diagnosis of AL is paramount for improving both short- and long-term morbidity and mortality. Identification of risk factors, the use of scoring systems, imaging techniques and routine use of biomarkers can help surgeons to establish an accurate and timely diagnosis of AL after colorectal surgery. The proper selection of the operation technique, preparation of the patient and administration of antibiotics can further improve the results and can lead to decrease of AL rates.

Conflict of Interests

Authors have no conflict of interest to disclose.

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