



Current State of the Problem of Colonic Anastomotic Leakage (Review)

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ABSTRACT: The authors of the article cite literature data on the annual incidence of the colon of about 2 million cases with a mortality rate of 25-30%, which is due to the growth of oncological diseases, varying degrees of equipment of institutions dealing with colorectal surgery, various techniques of performing operations, the method of forming anastomoses, and management of the postoperative period. At the same time, the colonic anastomotic leakage (CAL) is noted up to 20-30%.

The authors analyzed in detail the current state of the CAL problem on the basis of the analysis, including the meta-analysis of a number of researchers, who state the influence of many factors, as well as the state of the patient's body in the development of this complication.

The authors conclude that such a large number of factors, a number of which can be combined, as well as insufficient qualification of the surgeon, significantly complicate the task of developing recommendations for the prevention of CAL.

KEYWORDS: Colonic Anastomotic Leakage; Insufficiency of Sutures of Intestinal Anastomoses; Insufficiency of Sutures of the Colonic Anastomosis; Prevention, Surgical Treatment; Risk Factors.

The current stage of development of medical science is characterized by the growth of a number of malignant and benign pathologies of the colon, with an annual incidence of about 2 million cases and a mortality rate of 25-30% [1; 3].

Despite efforts to understand and prevent colonic anastomotic leakage (CAL), the incidence remains consistently high, and concomitant septic complications and prolonged hospitalization of patients may lead to delayed adjuvant therapy or even to the elimination of therapy for the underlying pathology of the large intestine, which may affect outcomes.

In the literature, there is a significant divergence of opinions regarding the frequency of specific postoperative complications in tumor pathology of the colon, which is due to the varying degrees of equipment of institutions dealing with colorectal surgery, various techniques of performing operations, the method of forming anastomoses, and the management of the postoperative period [2]. The frequency of CAL differs depending on the site of the anastomosis: with ileo-colonic anastomosis - from 0.5% to 6%, colocolonic anastomoses between - up to 9% and colorectal anastomoses - up to 20% [13; 16].

Patient-related prognostic factors can be divided into two categories: non-modifiable factors and modifiable factors. Several reviews have pointed to the following factors for the development of CAL: male gender, classification of physical status according to ASA, alcohol and tobacco use, comorbidities, obesity, malnutrition, hypoalbuminemia, steroid and non-steroidal anti-inflammatory drugs, neoadjuvant radiation therapy, neoadjuvant chemotherapy, use of neoadjuvant chemotherapy tumor stage, distal rectal tumor localization, blood transfusion and emergency surgery [24; 45].

Literature data on the influence of age, concomitant diseases, overweight, nutritional insufficiency, complicated tumor course, preventive intestinal stoma, preoperative chemoradiation treatment, intraoperative blood loss on the risk of CAL development are extremely controversial [8; 23].

Interestingly, the age of the patient is not a statistically significant factor in CAL. This conclusion has been confirmed by several large series of studies [9; 25]. However, patient age does correlate with increased mortality associated with CAL, with reported mortality rates of 5.2%, 18.3%, and 30.1% in patients under 65, 65-80, and over 80, respectively [9].

O.N. Shatrova et al. in the analysis of risk factors for insolvency of the sutures of the colonic anastomoses found that the frequency of its development does not depend on gender, age, technique of colonic anastomosis, the formation of an unloading colostomy, the content of fibrinogen and total blood protein before the operation and the type of preoperative preparation [5]. The



influence of the patient's nutritional status (proteinemia below 60 g / L) on the development of CAL has been confirmed in a number of studies [50].

P.V. Tsarkov et al. based on the data of the analysis of patients with rectal cancer after resection interventions, the male gender and low anterior resection were called statistically significant factors [4].

Multivariate analysis, carried out using several large series, showed higher CAL indices in male patients in the order of 1.38 to 3.5 times more often than in women [9; 25].

Obese patients and a BMI over 30 have a higher incidence of CAL in some studies, with odds ratios ranging from 2.2 to 3.78, compared with non-obese patients [8]. However, this conclusion is not supported by other large series of both univariate and multivariate analyzes.

There are few data on nutritional assessment as a risk of anastomotic leak [48]. Preoperative weight loss of more than 10% was defined as a predictor of anastomotic complications after ileocolic resection in Crohn's disease with an odds ratio of 6.23 (1.75-22.5) [7].

A recent prospective study of 3193 patients studying CAL after colon resection for cancer showed that obesity, preoperative total protein, male gender, ongoing anticoagulant treatment, and intraoperative complications are independent risk factors [18]. The results of this study led to the development of a CAL risk calculator using a modified nomogram [32]. The calculator aims to assist in preoperative patient counseling and surgeon decision making in order to provide a personalized patient management program. This calculator has not been tested yet and can be found at <http://anastomoticleak.com>.

In a large series of studies on data from the Dutch surgical colorectal audit of 15667 patients, higher CAL rates were reported in patients with ASA III and ASA IV compared to patients with ASA I and II (9.2 vs. 7.1%, $p < 0.001$) [9].

In patients with Crohn's disease, the risk coefficient for the development of CAL is 3.31 compared with patients without inflammatory bowel disease [25]. Patients with Crohn's disease taking steroids (defined as preoperative steroid use lasting more than 3 months) have an odds ratio of 5.95 (1.04–34.1) in the development of septic complications and CAL [48]. In a cohort of patients receiving steroids for pulmonary pathology, a significant association was found between steroid use before and during surgery and CAL [41]. In contrast, the use of immunomodulators such as azathioprine was not associated with an increase in anastomotic complications [42].

A recent systematic review of Crohn's disease patients undergoing surgery while receiving an anti-TNF agent showed a moderate increase in abdominal septic complications, OR 1.47 (1.08–1.99) [49].

Non-steroidal anti-inflammatory drugs (NSAIDs) are often included in postoperative accelerated recovery protocols as opioid-sparing agents. A recent systematic review of NSAIDs use suggests an association with CAL ($p = 0.030$). This association was not observed with selective COX-2 inhibitors [12].

The results of the Dutch Colorectal Cancer Treatment Group showed no significant difference in the incidence of CAL between the neoadjuvant radiation therapy group (11%) and the non-radiotherapy group (12%), which considered short-term radiation therapy [26].

Studies have shown that the risk of CAL in rectal anastomoses is directly related to their height above the edge of the anus, while the incidence of CAL is 1.7%, 4.1% and 7.3% with high, low and ultra-low anterior resections, respectively [16].

The very definition of CAL also differs in the literature and even among specialists. Meta-analysis J. Bruce et al. [14] showed that only 29 of the 47 studies reporting CAL included a definition that ranged from the presence of an abscess or fecal drainage and discharge to signs of peritonitis and extravasation of contrast agent.

In a study by K. Adams et al. [6] A survey of surgeons regarding their definitions of CAL showed that 94.2% of surgeons agreed that contrast extravasation was an anastomotic leak and 91.8% that fecal material in wounds or drains was CAL regardless of surgery.

The International Rectal Cancer Group has proposed a definition of CAL specifically related to anterior resection as “communication between the intraluminal and extraluminal regions due to a defect in the integrity of the intestinal wall during anastomosis between the colon and rectum or colon and anus” [30].

An inevitable interaction between the patient's physiology and technical factors predisposing the patient to CAL [15]. Several studies have identified risk factors for CAL, the identification of which before surgery is an important step in treatment, allowing you to influence modifiable factors and adapt the surgical technique.



Contamination of the anastomosis with microbial digestive flora is considered a major contributing factor to CAL. Many bowel prep aids are commonly used to reduce bacterial translocation. Meanwhile, their contribution to the prevention of CAL remains uncertain [21]. The importance of mechanical bowel preparation before colorectal surgery was assessed in a meta-analysis including 7 randomized controlled trials published by K. Slim et al. [35], who concluded that mechanical bowel preparation prior to colorectal surgery significantly increases the incidence of CAL.

More recently, in a second meta-analysis, K. Slim et al. [36], including 7 additional other randomized trials with 4859 patients, the authors concluded that there was no significant difference between the mechanical bowel preparation group and the non-mechanical bowel preparation group with regard to the prevention of CAL and intra-abdominal abscess [36]. In 2018, in a meta-analysis of 36 studies, 23 of which were randomized (level 2A), K.E. Rollins et al. [31] concluded that mechanical bowel preparation prior to colorectal surgery did not reduce the incidence of CAL.

Over the past decade, many studies have highlighted the importance of oral antibiotics in lowering CAL levels. Thus, S. Sadahiro et al. [33] in a study of 310 patients randomized into 3 groups (oral antibiotic decontamination, probiotic use, and control group), demonstrated that preoperative oral antibiotics significantly reduced the incidence of CAL in patients after elective surgery for colon cancer (1%-12% and 7.4%, respectively).

Also, K.E. Rollins et al. [31] in their meta-analysis of 40 studies, of which 28 were randomized with 69,517 patients, concluded that mechanical bowel preparation associated with oral antibiotic decontamination significantly reduced the incidence of CAL compared with the group who had exclusively mechanical preparation of the intestines.

It is generally accepted that collaboration between surgeons and anesthesiologists improves postoperative outcomes after colorectal surgery. It has been suggested that many intraoperative anesthesia-related factors are risk factors for CAL.

In a systematic review by E.C. Vasiliu et al. [45] reports that intraoperative blood transfusion increases the risk of CAL.

S.J. Van Rooijen et al. [43] confirmed this statement and reported many other factors (multimodal analgesia, optimal intraoperative fluid therapy, use of vasoactive drugs, and oxygen therapy) that improve early postoperative outcomes without any impact on the risk of CAL.

The minimally invasive approach to colorectal surgery has become the gold standard for benign and malignant colon diseases.

Two meta-analyses (grade 2A) [15] compared the laparoscopic approach with the conventional approach for hemicolectomy for cancer and showed no difference in the incidence of CAL between the two approaches. Another meta-analysis [20] comparing laparoscopic and traditional approaches to transverse colon resection also did not demonstrate any differences in the incidence of CAL between the two approaches. With regard to rectal surgery, according to H. Scheidbach et al. [39] The laparoscopic approach may be associated with a higher theoretical risk of CAL, especially in obese patients.

In a meta-analysis of randomized trials published by C. Simillis et al. [37] compared different approaches to anterior rectal resection. Twenty-nine randomized trials were included. The authors concluded that the approach does not affect the risk of developing CAL.

Despite the multifactorial nature of the causes, perfusion disorders and technical defects are considered the main factors of anastomotic leak. Consequently, in some patients, the level of vascular ligation may affect blood flow at the level of the anastomosis and prevent it from healing. This problem arises especially in tumors of the sigmoid and rectum, where high ligation of the inferior mesenteric artery can interfere with vascularization of the proximal end of the anastomosis.

In research by M.B. Si et al. [38], comparing high and low ligation of the inferior mesenteric artery in sigmoid or rectal cancer, concluded in favor of low ligation in terms of preventing anastomotic dehiscence. There was no difference in the timing of cancer outcomes (local recurrence, overall survival at 5 years, and relapse-free survival at 5 years).

Since the inception of the concept of image-guided surgery, several studies have evaluated the interest in fluorescence during colorectal surgery. In a meta-analysis published by R. Shen et al. [34], including 4 controlled clinical trials with 1177 patients, the authors concluded that the use of indocyanine green can significantly reduce the risk of CAL. However, there was heterogeneity between the different studies. In this report, fluorescence facilitated the modification of surgical technique in 4.7–16.4% of cases and allowed to expand the boundaries of resection in 19% of patients [11]. However, these results were not confirmed by the multicenter randomized trial published by P. De Nardi et al. [17]. This study included 240 patients. The authors concluded that the fluorescence of the dilated resection margin in 13 patients (11%) did not lead to a significant decrease in the incidence of CAL.



O.N. Shatrova et al. [5] found that “the use of precision thermometry in the preoperative period in patients with benign and malignant diseases of the colon in 77% of cases allows detecting violations of the endothelial mechanism of regulation of the vascular bed (endothelial dysfunction), in which complications in the early postoperative period”.

R. Warschkow et al. [46] based on the analysis of treatment of 527 patients undergoing intra-abdominal resection of the rectum for cancer, the statistically significant factor influencing the development of CAL, called intraoperative blood loss and the height of the tumor from the anus.

So, when analyzing the data of 110 212 patients, carried out by H.C. Pommergaard et al. [29], established the influence of radiation therapy on the development of CAL, while B. Garlipp et al. [19] did not find a connection between the development of CAL and chemoradiation therapy, which was administered to 2085 patients.

C.B. Neutzling et al. [27] in a meta-analysis of randomized controlled trials involving 1233 patients after colorectal surgery and comparing hand-stitched anastomoses with stapled staples, concluded that there was no difference between the two methods in terms of radiological and clinical CAL. However, this meta-analysis did not compare individual anastomoses, representing a bias associated with differences in vascularization, differences in gut lumen diameter, and differences in reconstruction technique between ileo-colic, colo-colic, colorectal anastomoses and after colostomy closure. When studying the effect of adhesives, protective films and other means on the prevention of CAL, no significant differences were found [1; 28].

A systematic review of six studies comparing single-layer (299 patients) and two-layer suture anastomoses (371 patients) showed no difference in the incidence of CAL [40]. The conclusion drawn supports the technique of one-layer sewing by hand, taking into account the shortened operation time.

Comparison of intracorporeal anastomosis with extracorporeal anastomosis is the subject of ongoing debate. Two meta-analyses compared these 2 methods in terms of the risk of developing CAL [44; 47]. The authors found no difference in favor of either technique. These results are consistent with 4 randomized trials published later [10].

CONCLUSIONS

Such a large number of factors, a number of which can be combined, as well as insufficient qualification of the surgeon, significantly complicate the task of developing recommendations for preventing suture insufficiency. In cases of already existing insufficiency, the patient's cure largely depends on the timing of the development of this complication, the nature of the intestinal discharge, its amount, as well as the correct treatment tactics. Even with all the measures taken to prevent failure and their treatment, there is no complete guarantee of regression of the pathological process.

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