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Preventive strategies for anastomotic leakage after colorectal resections: A review

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Abstract

Anastomosis is a crucial step in radical cancer surgery. Despite being a daily practice in gastrointestinal surgery, anastomotic leakage (AL) stands as a frequent postoperative complication. Because of increased morbidity, mortality, combined with longer hospital stay, the rate of re-intervention, and poor oncological outcomes, AL is considered the most feared and life-threatening complication after colorectal resections. Furthermore, poor functional outcomes with a higher rate of a permeant stoma in 56% of patients this could negatively affect the patient's quality of life. This a narrative review which will cover intraoperative anastomotic integrity assessment and preventive measures in order to reduce AL. Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis, surgeons have proposed several preventive measures, which were assumed to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative air leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, lack of clear evidence of which preventive measures is superior over the other combined with the fact that the decision remains based on the surgeon's choice. Despite the advances in surgical techniques, AL remains a serious health problem associated with increased morbidity, mortality with additional cost. Many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. MBP combined with oral antibiotics still recommended.

Key words: Anastomotic leakage; Colorectal; Resection; Anastomosis; Cancer; Anastomotic disruption

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Core tip: Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis, surgeons have proposed several preventive measures, which were assumed to reduce the incidence of anastomotic leakage, including antibiotic prophylaxis, intraoperative air leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, the decision remains based on the surgeon's choice. This review found that many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. Mechanical bowel preparation combined with oral antibiotics still recommended.

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INTRODUCTION

Anastomosis is a crucial step in radical cancer surgery. Despite being a daily practice in gastrointestinal (GI) surgery, anastomotic leakage (AL) stands as a frequent postoperative complication^[1]. A recent analysis of the National Surgical Quality Improvement Program (NSQIP) database reported that rectal anastomoses were associated with the greatest incidence of AL attributing this to lacking serosa, the under tension anastomoses, technical difficulties in working in the deep pelvis, and easily compromised blood supply^[2,3].

Because of increased morbidity, mortality, combined with longer hospital stay, the rate of re-intervention, and poor oncological outcomes, AL is considered the most feared and life-threatening complication after colorectal resections. Furthermore, poor functional outcomes with a higher rate of a permeant stoma in 56% of patients this could negatively affect the patient's quality of life^[4-6].

Rojas-Machado *et al*^[7] in a trial to develop a prognostic index for colorectal AL, they found that 54 potential risk factors were present in the literature. The two most common factors associated with a significantly higher risk of AL were anastomotic height, followed by male sex^[8,9]. So, the incidence of AL following colorectal resections varies according to the anastomotic level, being 1% to 19% in colorectal or coloanal anastomoses; 0% to 2% in colocolic anastomoses; 0.02% to 4.0% in ileocolic anastomoses; and around 1% in ileoileal anastomoses^[10-14].

Surgeons advocated several surgical measures in order to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. Controversy still exists, which preventive measure is superior over the other combined with the fact that the decision remains based on the surgeon's choice^[15,16].

This review will cover intraoperative anastomotic integrity assessment and preventive measures in order to reduce AL.

INTRAOPERATIVE ANASTOMOTIC INTEGRITY

Nachiappan *et al*^[17] in a systematic review of intraoperative tests for the assessment of colorectal anastomotic integrity, they testified a reduction in the AL rate when these tests were applied and they divided these tests into: (1) Mechanical patency assessment including air or dye leak testing competence of the doughnuts, it tests the anastomosis by occluding proximal to the anastomosis followed by transanal filling with air or dye to assess any leaking point into the peritoneal cavity without permitting direct anastomotic inspection; (2) Endoscopic visualization which permits direct inspection with the possibility of therapeutic intervention; and (3)

Microperfusion methods permitting blood flow analysis or tissue perfusion showing oxygenated and deoxygenated hemoglobin and the properties of feeding vessels which in turn may modify the planned anastomotic site or reinforce it if needed^[4].

Intraoperative anastomotic air leak testing

Wu *et al*^[18] in a systematic review of the value of intraoperative leak test in prevention of colorectal AL they testified variable methods for performing air leak test (ALT) with variable volume of inflated gas/dye, while ALT group had a lower AL rate compared to the non-ALT group, however, this was non-significant. Patients with positive-ALT had a significantly higher clinical AL rate compared to those with negative-ALT. Additional sutures or diversion were applied to positive-ALT patients. Despite it does not reduce AL, they recommended the routine performance of ALT as it at least predicts high-risk anastomosis and allows additional repairs.

Evaluation of anastomotic perfusion “Microperfusion”

Traditionally, surgeons rely on active mucosal bleeding, the bright coloration, and palpable mesenteric pulses as indicators of adequate perfusion. The search for a reliable objective method to determine tissue perfusion intraoperatively was warranted in order to reduce the incidence of AL, different modalities were applied, however, none has been used routinely in clinical practice^[19].

Recently, Near-Infrared (NIR) Fluorescence Angiography using Indocyanine Green (ICG) which is a tricarbo-cyanine molecule when it is injected intravenously, it remains confined to the intravascular space due to its hydrophobic properties allowing it to bind strongly to the plasma proteins. It also fluoresces when excited by light of a particular frequency due to its fluorophoric properties, so it can be used intraoperatively for LN mapping with higher sensitivity and specificity^[20] as well as in intraoperative perfusion assessment using NIR light technology^[21].

Mizrahi and Wexner^[22] in a review about the role of NIR of the colorectal anastomosis using ICG they reported 3.7%-19% change in the intraoperative decision with further proximal resection for the hypo-perfused anastomoses. They found 6 series with more than 100 patients showed a lower incidence of AL by 4%-12% compared to 75% published case-control series. Jafari *et al*^[23] in the PILLAR II trial using NIR ICG in distal colorectal resections, they concluded its safety and feasibility. Degett *et al*^[24] in a systematic review of the role of ICG Angiography for intraoperative perfusion assessment of GI anastomoses they testified regarding the colorectal anastomoses after colorectal cancer, that ICG Fluorescence Angiography had a significant lower AL rate compared to those without assessment. Similar results were reported by studies^[25,26].

PREVENTIVE MEASURES

Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis^[27], surgeons have proposed several preventive measures, which were assumed to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative ALT, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, the decision remains based on the surgeon's choice^[1,28].

Mechanical bowel preparation

Traditionally, mechanical bowel preparation (MBP) through the last century was believed to be an important factor within the control of surgeons in order to reduce AL rate and infectious complications in elective colorectal surgery^[29]. MBP was proposed to have a few theoretical advantages; decreasing the fecal bacterial count, which in turn decrease infectious complications, easier bowel manipulation, decrease the risk of unwanted spillage into the abdomen, decrease the chance of mechanical disruption of the anastomosis^[30].

Slim *et al*^[31] in a meta-analysis of RCTs comparing colorectal surgery with or without prophylactic bowel preparation, they reported a significant AL rate in bowel preparation group. Furthermore, they recommended what was mentioned 40 years ago by Hughes^[32], “Omission of enemas and bowel washes from the preoperative procedures will be welcomed by both patients and nursing staff”.

Güenaga *et al*^[33] in a Cochrane systematic review including a total of 5805 patients, there was not a significant evidence support the use of both MBP or rectal enemas. Additionally, bowel preparation can be omitted safely from colonic surgery, while few studies suggested its selective application in rectal surgery without known significant value. Anastomosis below the peritoneal reflection and laparoscopic rectal surgery still warranted further research^[33].

Oral antibiotics

The concept of the use of oral antibiotics in order to reduce the AL was shown by Cohn and Rives^[34] in 1955 in the animal model with a complete devascularization of the anastomotic site, the dogs which received oral antibiotics completely recovered with both serosa and mucosa were normal grossly and microscopically, while the control dogs died rapidly from perforated devascularized segment and fecal peritonitis.

Roos *et al*^[35] in a systematic review and meta-analysis of RCTs about the selective decontamination of the digestive tract (SDD) using a combination of oral antibiotics in addition to intravenous antibiotics compared to intravenous antibiotics alone in elective GI surgery. They testified a significantly lower rate of AL in SDD, a further subgroup analysis for both upper and lower GI surgeries with SDD associated with reduced the incidence of AL in both subgroups.

Recently, data from the NSQIP by Scarborough *et al*^[36] in a study aimed to determine the association between preoperative bowel preparation status and 30-d outcomes in including AL after elective colorectal resection, with a total of 4999 patients; 1494 patients received combined MBP and oral antibiotic preparation (OAP), 2322 MBP only, 91 OAP only, and 1092 no preoperative preparation. Patients in the combined MBP and OAP group had significantly the lowest incidence of postoperative AL (2.8%) compared to 5.7% of no preparation group, this significance was maintained after adjustment. Patients receiving MBP only or OAP only did not differ significantly from those did not receive preparation^[36]. Similar results from NSQIP testified by Kiran *et al*^[37] a total of 8442 patients, 3822 received MBP only, 2324 combined MBP and antibiotic, 2296 no preparation. On multivariate analyses, MBP with antibiotics compared to no preparation was independently associated with lower AL.

A recent pan-European study contacted by the European Society of Coloproctology collaborative group on 3676 patients from 343 centers across 47 countries who underwent left-sided colorectal resections. In this study 29.9% of the patients received no MBP, 52.9% received MBP only, and 16.8% received MBP plus oral antibiotics (Abx). In the multivariate analysis, MBP plus Abx was the only group with a lower risk of AL (OR 0.52, 0.30-0.92, $P = 0.02$)^[38].

Creation of the anastomosis

Creation of an anastomosis is a hallmark of surgical practice, decades of practice and research brought a large variety of techniques which made it difficult when trying to conclude about the safest method^[39].

Stapled vs hand-sewn anastomosis: Stapled anastomoses were believed to have a better healing and less operative complications in comparison to hand-sewn anastomoses, this was explained by less tissue manipulation and better blood supply^[40]. MacRae *et al*^[41] in a meta-analysis found no significant difference in total, clinical, and/or radiological AL between stapled and hand-sewn colorectal anastomoses. Lustosa *et al*^[42] in a systematic review and meta-analysis of RCTs comparing stapled and hand-sewn anastomoses, irrespective of the level of colorectal anastomosis they were not able to address any superiority of stapled over hand-sewn anastomosis. The same conclusion was reported by Neutzing *et al*^[43] in a Cochrane Systematic Review.

Slieker *et al*^[39] in a systematic review of evaluating the technique of colorectal anastomosis with the clinical AL as the outcome measure, they found a level 1A evidence that there was no superiority between stapled and hand-sewn anastomoses. They also concluded that the hand-sewn anastomoses were constructed following an undefined technique, while the stapled anastomoses were much more uniform.

Compression anastomoses: Stapled or hand-sewn anastomoses both are characterized by the use of foreign material; the persistent existence of these foreign materials can be avoided by the use of compression anastomosis with a resultantly reduced inflammation which in turn decrease the duration of the lag phase of anastomotic healing^[44]. A revolution took place starting from a silver ring by Denans in 1826, then in the Murphy button in 1892 by Murphy. In the 1980s, the ValtracTM in colorectal anastomoses with the use of biofragmentable anastomotic ring by Hardy *et al*^[45] in 1984, AKA-2 and subsequently the AKA-4 modification for transanal application in the lower rectal anastomoses using non-absorbable metal pins by Kanshin and colleagues in Russia. Recently in colorectal anastomose using nickel-titanium either a clip alloy (Compression Anastomosis Clip-CAC) or a ring compression device (Compression Anastomosis Ring-ColonRing)^[44,45]. Slieker *et al*^[39] testified a level 1B evidence similarity between hand-sewn and compression anastomoses.

The colonic J-pouch: A lower incidence of AL was testified between colonic J-pouch anastomosis and straight anastomosis^[46-48]. Justifications of this difference in AL came from the idea that creation of the J-pouch necessitates the full mobilization of the splenic flexure and the obliteration of the pelvic dead space by the colon^[49]. Later, Hallböök *et al*^[46] considered the microcirculation difference at the anastomotic site between straight coloanal anastomosis and colonic J-pouch anal anastomosis. They settled a favorable healing anastomosis in the colonic J-pouch compared to colonic end in the straight coloanal anastomosis, due to unaffected blood flow at the anastomotic site of the pouch, whereas became relatively ischemic at the colonic end in the straight coloanal anastomosis.

Brown *et al*^[50] in a Cochrane systematic review of the reconstructive techniques after rectal resection for rectal cancer they testified that colonic J-pouch leads to better bowel function and similar rates of postoperative complications when compared to the straight coloanal anastomosis. While there is limited literature comparing the transverse colectomy procedure to the colonic J-pouch, three small RCTs suggested that bowel function was similar in patients reconstructed with either procedure. However, there is some evidence that the transverse colectomy procedure results in more AL. Liao *et al*^[51] in a meta-analysis comparing colonic J-Pouch vs transverse colectomy pouch after AR for rectal cancer, they found no significant difference in the incidence of AL. Hüttner *et al*^[52] in a meta-analysis of the reconstruction techniques after LAR for rectal cancer they reported that there is no significant difference between straight or side-to-end coloanal anastomosis, colonic J pouch, and transverse colectomy.

Coating of the anastomosis

It was proposed that external coating of the anastomosis with various materials may reduce clinical AL, especially for high-risk anastomoses as the coating material will seal off the defect. Pommergaard *et al*^[1] in a systematic review to evaluate the external coating of colonic anastomoses, they reported variable materials had been used with contradictory results, this may be due to the fact that most of these series were studied in experimental animals of different species and of different designs, so their role remains unclear. Only fibrin sealant, omental pedicle graft, and hyaluronic acid/carboxymethylcellulose have been testified in humans.

Fibrin sealant: Vakalopoulos *et al*^[53] in a systematic review of the use of tissue adhesive in GI anastomoses they found it difficult to draw a conclusion on the effects of the tested tissue adhesives on each level of GI anastomosis due to too much heterogeneity in the animal model, absence of details of the amount or the method of applied sealant, and the anastomotic technique was not standardized. They reported 9 studies in rats on fibrin sealant showed to decrease the incidence of AL. The only report on human by Huh *et al*^[54] in a non-randomized trial of patients who underwent laparoscopic LAR for rectal cancer without diversion, they compared 104 patients in whom fibrin sealant was applied to intracorporeal stapled anastomosis to 119 patients without the use of fibrin sealant was not found to decrease the incidence of AL. They did not describe the amount of the sealant. Nordentoft *et al*^[55] in a systematic review to assess the potential effect of fibrin sealant on the healing of GI anastomoses, they indicated that it is a physical and mechanical effect neither due to improving the healing power of the anastomosis.

Omental pedicle graft (Omentoplasty): A controversy still exists over the use of omentoplasty to decrease the AL rate after colorectal resection^[56]. Wrapping the anastomosis with intact or pedicled omentum has been designated since 1977 in order to reduce the rate or the severity of AL after colorectal resections, however, insufficient randomized controlled trials exist with conflictive results such as necrosis of the wrap and anastomotic stricture^[56,57]. Theoretically, when resections are performed for cancer, omentoplasty patients are exposed to further risks of radiation necrosis and local recurrence which was described recently in the animal model^[57].

Hao *et al*^[58] in a meta-analysis of the role of omentoplasty in the prevention of AL after colorectal resection found that there is no supportive evidence to use or not to use omentoplasty as a measure to reduce AL after colorectal resection. Wiggins *et al*^[59] in a systematic review and meta-analysis in GI anastomoses, they testified on three RCTs of colorectal anastomoses, there was no significant difference in the incidence of AL nor the in-hospital mortality.

The defunctioning stoma

The value of defunctioning stoma is still controversial, the debate is still present, whether AL rates are lower in diverted anastomoses in comparison to non-diverted anastomoses or both are similar^[60-62]. Many surgeons delineated the routine use of

proximal diversion for poor patient general condition, narrow male pelvis, neoadjuvant chemoradiotherapy, intraoperative complications related to the anastomosis, low-lying rectal cancer with total mesorectal excision (TME), the goal was to divert the fecal stream from the anastomotic site, which in turn could reduce the incidence of AL and its related morbidity^[63,64].

Tan *et al*^[65] in a meta-analysis about the role of the defunctioning stoma in LAR for rectal cancer testified that value conferred by defunctioning stoma in decreasing the rate and in mitigating the severity of AL. Hüser *et al*^[60] in a systematic review and meta-analysis of the role of the defunctioning stoma in low rectal cancer surgery, they reached the same conclusion with a significantly lower AL and reoperation rates, whereas mortality rates remained comparable between the groups. These results also were verified by Montedori *et al*^[61] in a Cochrane systematic review about the use of covering stoma in anterior resection for rectal cancer. Matthiessen *et al*^[9] in a study of risk factors of AL after rectal resection concluded that in the presence of intraoperative adverse events, defunctioning stoma did not decrease the risk of symptomatic AL. Despite many surgeons delineates a concept of diverting colorectal anastomosis, a controversy still stands whether the best defunctioning could be achieved by loop ileostomy or loop colostomy to address this controversy Güenaga *et al*^[62] in a Cochrane systematic review found it is not possible to express a preference for use of either loop ileostomy or loop colostomy^[62].

However, these benefits must be justified by the fact that routine stoma creation will reduce the quality of life in patients in whom leakage will not occur, the stoma itself is a source of high morbidity reach up to 30%^[66]. Moreover, the stoma reversal is associated with a mortality of up to 2.3%, requires a second reintervention and hospital readmission^[60,67-69]. Chow *et al*^[70] in a systematic review about the morbidity of the reversal of defunctioning ileostomy, they testified that an underestimation of the consequence of stoma reversal. They recommended a selective use of defunctioning ileostomy with patient counseling about the possible complications of reversal at the time of the initial operation. Lindgren *et al*^[5] in a multicenter RCT about the risk of permeant stoma after LAR for rectal cancer, 234 patients randomly assigned to defunctioning stoma ($n = 116$) or a group without defunctioning stoma ($n = 118$), they testified that 19% of patients their stoma became permanent and this risk was significant for those who developed AL 56% compared to 11% for those without AL.

Pelvic drainage

The purpose of pelvic drainage is to obliterate the pelvic dead space preventing the accumulation of fluid or blood which in turn may form a pelvic abscess or infected pelvic hematoma, both may erode through the anastomosis. Pelvic drainage also may permit the early detection of AL. Some surgeons adopted the use of routine pelvic drainage, other surgeons place drain only in case of doubt about the quality of the anastomosis^[71]. Pelvic drainage was believed not to prevent AL, nevertheless, the drain serves as “an eye” into the pelvis, allowing for early detection of silent leakage of feculent, pus, or air. It also may contribute to the conservative management of AL^[3].

Tsujinaka and Konishi^[72] in a review article about the usage of drainage in colorectal surgery, they testified that the use of drain should be justified against its own related complications like drain-site infection (up to 2.5%), pain, bleeding, bowel evisceration or injury (0.1%-0.5%), and omental herniation (up to 1.0%). Placing the drain may even disrupt the anastomosis itself. Smith *et al*^[73] in the animal model showed the danger of placing latex drains near to a colonic anastomosis, as this was associated with a significantly higher incidence of AL, they assumed that latex seems to have a local inhibitory effect on anastomosis healing process. Urbach *et al*^[74] in meta-analysis and systematic review testified that the use of prophylactic drain has no benefit in prevention of AL or even controlling it if occurs. Jesus *et al*^[71] in a Cochrane systematic review of RCTs about the role prophylactic anastomotic drainage for colorectal anastomoses they testified this practice devoid evidence. Petrowsky *et al*^[75] in a systematic review and meta-analysis testified that AL was not significantly different between drained and no drained anastomoses. Rolph *et al*^[76] reported the same results in another Cochrane review.

On the other hand, Zhang *et al*^[77] in a systematic review of the use of prophylactic pelvic drainage in colorectal anastomosis to reduce postoperative complications. They testified that no statistically significant difference between the drain and the no drain groups in term of clinical or radiological AL. An unclear value of draining extraperitoneal anastomosis was testified by Rondelli *et al*^[78] in a meta-analysis, they revealed a lower incidence of AL in drained anastomosis than in the non-drained anastomosis, furthermore, a significantly lower rate of reintervention was found in the drained group than in the non-drained. Karliczek *et al*^[79] in a systematic review and a meta-analysis on RCTs generally testified that there is no significant difference in the occurrence of clinical or radiological AL. According to the anastomotic level,

they reported no benefit of extraperitoneal anastomosis drainage, but this was based on 2 RCTs.

Transanal tube drainage

The transanal tube drainage may potentially lower the incidence of AL and its clinical consequences this may be attributed to direct drainage, decreasing the intraluminal pressure and promotion of motility^[80]. Lee *et al*^[81] investigated the impact of using a transanal tube drainage after LAR without defunctioning stoma on the incidence of AL, when a propensity score matching was applied the incidence of AL in patients with transanal tube drain had a lower incidence of AL with a reduced number of patients with peritonitis, however, all these difference did not reach significant level.

Shigeta *et al*^[82] in a meta-analysis tested that transanal tube drainage was associated with a significantly lower rate of AL and reoperation compared with those without. Wang *et al*^[83] recently in a systematic review and meta-analysis based on three observational studies and one RC, they testified that transanal tube drainage associated with a significantly lower incidence of AL and reoperation with unknown mechanism may be attributed to the reduced intraluminal pressure. Ha *et al*^[84] in a systematic review and meta-analysis about the role of transanal tube placement after LAR for rectal cancer in RCTs of 475 patients they testified no difference between both groups, while in non-randomized studies of 643 patients the placement of transanal tube was associated with a lower incidence of AL.

CONCLUSION

Despite the advances in surgical techniques, AL remains a serious health problem associated with increased morbidity, mortality with additional cost. Many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. MBP combined with oral antibiotics still recommended.

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