Risk Factors for Anastomotic Leak Following Colorectal Surgery

A Case-Control Study

Dana A. Telem, MD; Edward H. Chin, MD; Scott Q. Nguyen, MD; Celia M. Divino, MD

Objective: To assess anastomotic leak (AL) risk factors in a large patient series.

Design: Case-control study.

Setting: The Mount Sinai Hospital.

Patients: Ninety patients with AL following colorectal resection and 180 patients who underwent uncomplicated procedures.

Main Outcome Measures: Risk factors associated with development of AL.

Results: The AL rate was 2.6%. Five risk factors for AL were identified: (1) preoperative albumin level lower than 3.5 g/dL (odds ratio [OR] 2.8; 95% confidence interval [CI], 1.3-5.1) (P = .03); (2) operative time of 200 minutes or longer (OR, 3.4; 95% CI, 2.0-5.8) (P = .01); (3) intraoperative blood loss of 200 mL or more (OR, 3.1; 95% CI, 1.9-5.3) (P = .01); (4) intraoperative transfusion requirement (OR, 2.3; 95% CI, 1.2-4.5) (P = .02); and (5) histologic specimen margin involvement in disease process in patients with inflammatory bowel disease (IBD) (OR, 2.9; 95% CI, 1.4-6.1) (P = .01). Patients with all 3 intraoperative risk factors had an OR of 22.1; 95% CI, 2.8-175.4 (P < .001) for development of AL.

Conclusions: Histologic resection margin involvement in disease process in patients with IBD, preoperative albumin levels lower than 3.5 g/dL, intraoperative blood loss of 200 mL or more, operative time of 200 minutes or more, and/or intraoperative transfusion requirement increased AL risk. Enteral nutritional optimization prior to elective surgery is essential. Proximal diversion should be considered for patients with all 3 intraoperative risk factors because they are at high risk for AL.


Anastomotic leaks (ALS) are inevitable complications affecting 2% to 10% of patients undergoing gastrointestinal surgery.1-4 Substantial patient morbidity and mortality and poor long-term outcomes are ascribed to anastomotic dehiscence.5-8 Studies report additional patient morbidity rates ranging from 20% to 30% and mortality rates of 7% to 12%.5-8 In addition, development of a postoperative AL negatively impacts oncologic outcome in patients undergoing curative resection for colorectal cancer.6

See Invited Critique at end of article

Identification of patients at increased risk for anastomotic dehiscence is imperative for preoperative patient optimization and selective proximal diversion.5,10 While many studies have investigated patient, operative, and disease-specific factors associated with the development of postoperative AL, to our knowledge, no consensus on high-risk patient populations exists.11,12 This inconsistency is likely attributable to the limited study power of available AL literature. The purpose of the present study was to identify risk factors for the development of AL in the largest prospectively recorded series, to our knowledge, of patients with anastomotic dehiscence following colorectal surgery.

METHODS

Following approval by The Mount Sinai School of Medicine institutional review board, 90 patients with ALs treated between January 1, 2002, and December 31, 2007, were identified from a prospectively maintained administrative database. Complications occurring within 30 days of surgery are prospectively captured by our institution’s rigorously maintained online morbidity and mortality database. To ensure comprehensive reporting, the database is cross-referenced with incident reports generated by patient readmission or reoperation within 30 days of surgery.
days of the original procedure as well as institutionally measured quality performance indicators that include AL.

The hospital records of patients reported to have a diagnosis of AL, enterocutaneous fistula, intra-abdominal abscess or wound infection following ileocolostomy (Current Procedural Terminology [hereinafter “CPT”] codes, 44160 and 44205), partial colectomy with anastomosis (CPT codes 44140 and 44204), partial colectomy with coloprostectomy (CPT codes 44146 and 44208), and subtotal colectomy or restorative proctocolectomy with ileal–rectal or ileal pouch–anal reconstruction (CPT codes 44150, 44152, 44153, 44210, and 44211) were retrospectively reviewed. Anastomotic leak was defined by gross anastomotic dehiscence conferring feculent or purulent peritonitis or evidence of communication between anastomotic site and intra-abdominal abscess, wound, or fistula tract. Diagnosis of AL was confirmed by intraoperative findings or extravasation of enteric contrast from anastomotic site on radiographic imaging.

Eligible controls included patients who underwent uncomplicated gastrointestinal operations. Two control patients were paired to each case patient by procedure and surgeon. Control patients were identified from an administrative database using CPT codes for ileocolostomy (44160 and 44205), partial colectomy with anastomosis (44140 and 44204), partial colectomy with coloprostectomy (44146 and 44208), and subtotal colectomy or restorative proctocolectomy with ileal–rectal or ileal pouch–anal reconstruction (44150, 44152, 44153, 44210, and 44211) were retrospectively reviewed. Anastomotic leak was defined by gross anastomotic dehiscence conferring feculent or purulent peritonitis or evidence of communication between anastomotic site and intra-abdominal abscess, wound, or fistula tract. Diagnosis of AL was confirmed by intraoperative findings or extravasation of enteric contrast from anastomotic site on radiographic imaging.

Univariate analysis by unpaired t test with 2-tailed distribution was used for quantitative variables and χ² test for categorical variables. Multivariate logistic regression models were used to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs). Final multivariate models were created by elimination of nonsignificant variables from univariate analysis. P values of less than .05 for associations were considered to indicate statistical significance. Prism statistical software (April 2003) (Prism Software Corporation, Irvine, California) was used for all analyses. All analyses were reviewed with a statistician.

### RESULTS

Ninety patients of 3501 were identified with a diagnosis of AL after gastrointestinal surgery, conferring a 2.6% AL rate following the colorectal operation. Mean time to diagnosis of AL was 7.5 days after surgery and 8 deaths occurred (9%). Thirty-two ALs involved ileocolic anastomoses, 32 colorectal, 12 ileorectal, and 14 ileal–anal pouch anastomoses. A 2-to-1 match of control to case patients was performed. The control group comprised 64 ileocolic, 64 colorectal, 24 ileocolic, and 14 ileal–anal pouch anastomoses.

### PREOPERATIVE PATIENT RISK FACTORS

Univariate analysis demonstrated preoperative albumin level as significantly lower in patients who subsequently developed AL than it was in those who did not (mean [SD] albumin levels, 3.7 [0.6] mg/dL vs 4.1 [0.8] mg/dL (P = .02). (To convert albumin to grams per liter, multiply by 10.) Multivariate regression modeling demonstrated that a preoperative albumin level lower than 3.5 mg/dL had an OR of 2.8 (95% CI, 1.3–5.1) (P = .03) for AL development. An operative indication of colon cancer was associated with a decreased risk of AL development (26% vs 41%) (P = .01) with an OR of 0.51 (95% CI, 0.3–0.9) (P = .01). No significance on univariate analysis was demonstrated by patient demographics, comorbidity, social or surgical history, use of preoperative immunosuppressants, or operative indication other than colon cancer (Table 1 and Table 2).

### OPERATIVE RISK FACTORS

Univariate analysis identified intraoperative time (mean [SD] time 203.8 [58.3] minutes vs 156.9 [85.9] minutes) (P < .001), intraoperative blood loss (292.2 [353.3]...
Table 2. Results of Univariate Analysis of Patient Comorbidity, Operative Indication, and Preoperative Use of an Immunosuppressant

<table>
<thead>
<tr>
<th>Patient Comorbidity</th>
<th>Control (n=180)</th>
<th>AL (n=90)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>19 (11)</td>
<td>10 (11)</td>
<td>.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (43)</td>
<td>32 (36)</td>
<td>.24</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20 (11)</td>
<td>11 (12)</td>
<td>.64</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4 (2)</td>
<td>4 (4)</td>
<td>.44</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>26 (14)</td>
<td>17 (19)</td>
<td>.38</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>37 (21)</td>
<td>29 (32)</td>
<td>.06</td>
</tr>
<tr>
<td>COPD</td>
<td>5 (3)</td>
<td>2 (2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>6 (3)</td>
<td>1 (1)</td>
<td>.43</td>
</tr>
</tbody>
</table>

Table 3. Results of Univariate Analysis of Potential Intraoperative Risk Factors

<table>
<thead>
<tr>
<th>Intraoperative Risk Factor</th>
<th>Control (n=180)</th>
<th>AL (n=90)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA score, mean (SD)</td>
<td>2.3 (0.05)</td>
<td>2.4 (0.07)</td>
<td>.32</td>
</tr>
<tr>
<td>Operative time, mean (SD), min</td>
<td>156.9 (85.9)</td>
<td>203.8 (58.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood loss, mean (SD), mL</td>
<td>154.4 (199.1)</td>
<td>292.2 (353.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PRBC transfusion</td>
<td>20 (11)</td>
<td>20 (22)</td>
<td>.03</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>66 (37)</td>
<td>32 (36)</td>
<td>.96</td>
</tr>
<tr>
<td>Test of anastomotic integrity</td>
<td>94 (52)</td>
<td>48 (53)</td>
<td>.96</td>
</tr>
<tr>
<td>Operative technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>114 (63)</td>
<td>64 (51)</td>
<td>.07</td>
</tr>
<tr>
<td>Conversion</td>
<td>10 (9)</td>
<td>4 (9)</td>
<td>.98</td>
</tr>
<tr>
<td>Open</td>
<td>66 (37)</td>
<td>44 (49)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Table 4. Results of Univariate Analysis of Specimen Pathology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Control (n=180)</th>
<th>AL (n=90)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-to-end anastomosis</td>
<td>60 (100)</td>
<td>34 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Histologic specimen margin involvement in patients with IBD</td>
<td>13 of 63 (21)</td>
<td>20 of 46 (43)</td>
<td>.02</td>
</tr>
<tr>
<td>Presence of diverticula</td>
<td>37 (21)</td>
<td>16 (18)</td>
<td>.70</td>
</tr>
</tbody>
</table>

DISEASE-SPECIFIC FACTORS

Univariate analysis demonstrated that in patients with inflammatory bowel disease (IBD), histologic specimen margin involvement in disease process was increased in patients who developed subsequent ALs (43% vs 21%) (P=.02). Logistic regression demonstrated that histologic specimen margin involvement had an OR of 2.7 (95% CI, 1.2-6.4) (P=.01) for development of AL. End-to-end anastomosis donuts were noted to be complete on the pathology report in all specimens. Presence of colectomy in operative specimens did not increase risk of AL (Table 4). Table 5 provides a list of significant risk factors for AL development.

Anastomotic dehiscence is an infrequent yet often devastating complication of gastrointestinal surgery. Identification of patients at high risk for development of AL is essential for preoperative patient optimization and selective proximal diversion. Although proximal diversion abates patient presentation with severe consequences of dehiscence, selective use is cautioned secondary to the morbidity associated with ostomy formation, maintenance, and reversal. A recent prospective study demonstrated a morbidity rate of 25% and mortality rate of 2% in patients with low pelvic anastomoses who underwent reversal of protective loop ileostomy.

Risk factors for anastomotic dehiscence have traditionally been stratified into 3 categories: patient, operative, and disease-related factors. Following this model, the present study aimed to delineate patients at high risk for postoperative anastomotic disruption. Analysis of preoperative patient factors revealed that poor nutri-
tional status, as indicated by preoperative albumin levels lower than 3.5 mg/dL, conferred an increased risk for development of AL. This finding is corroborated by other studies that have demonstrated a correlation between low albumin levels and anastomotic dehiscence.\textsuperscript{17,18} In a study of 44 patients with AL, Makelä et al\textsuperscript{16} reported a serum albumin level below 35 g/L as a key risk factor. Poor preoperative nutritional status has long been implicated in the development of postoperative complications.\textsuperscript{20-22} Studies demonstrating improved surgical outcome in malnourished patients with adequate enteral caloric intake for 7 to 10 days preoperatively highlight the importance of preoperative nutritional optimization.\textsuperscript{20,21} Based on study results and available literature, we recommend enteral nutritional optimization prior to elective surgery. In the absence of severe patient malnutrition, routine use of preoperative parenteral nutrition is not recommended.\textsuperscript{20,22}

Assessment of operative indication demonstrated a reciprocal association between colon cancer and AL development. Wide resection margins to healthy, uninvolved tissue coupled with strict adherence to resection along anatomic blood supply may decrease risk of AL by ensuring adequate vascular supply to the newly constructed anastomosis. In contrast, an operative indication of rectal cancer did not influence risk for development of AL. While reports vary, tumor distance from the anal verge is a recognized risk factor for development of anastomotic dehiscence.\textsuperscript{19-22} A study of 35 patients demonstrated that resection of rectal tumors 12 cm or less from the anal verge conferred an increased risk of AL.\textsuperscript{31-35} We found only 1 study that demonstrated intraoperative blood pressure lability, hand-sewn vs stapled completion of anastomosis, laparoscopic vs open operative technique, and performance of proximal diversion should strongly be considered for this subset of patients.

Assessment of additional intraoperative variables demonstrated that intraoperative blood pressure lability, hand-sewn vs stapled completion of anastomosis, laparoscopic vs open operative technique, and performance of intraoperative testing of anastomotic integrity did not influence AL rate.

Univariate and multivariate analysis demonstrated that in patients with IBD, microscopic specimen margin involvement in inflammatory disease process correlated with an increased risk of AL.\textsuperscript{31-35} Pennington et al\textsuperscript{30} reported an identical incidence of immediate postoperative anastomotic dehiscence in patients with microscopically normal vs diseased resection margins (3 of 52 [6%] vs 3 of 51 [6%]).\textsuperscript{39} Although the authors concluded that an association between AL and microscopic resection margin involvement in Crohn disease was unlikely, the low sample size precluded significance.\textsuperscript{33} In the present study, statistical significance was achieved, indicating that histologically diseased specimen margins in patients with IBD increased AL risk (OR, 2.7) (P = .02). While wider resection margins in patients with IBD are not advocated, heightened clinical suspicion for postoperative AL as well as consideration of proximal diversion with grossly diseased bowel at the anastomotic site is recommended.\textsuperscript{37}

The development of AL remains unpredictable in many patients. However, herein we identify several significant patient, operative, and disease-specific risk factors. Preoperative nutritional optimization as well as minimization of intraoperative time, transfusion requirement, and blood loss are essential to decrease the risk of anastomotic dehiscence. Pathologic specimen reports indicating microscopic margin involve-
ment in patients with IBD should heighten physician awareness for the possibility of a postoperative AL.

The strengths of this study include the sample size, case-control patient match, and prospective collection from an AL database. Study limitations include the inherent variability in operative technique and patient management associated with multiple surgeons as well as non-uniformity of surgical indications.

In conclusion, while the development of AL remains unpredictable in many patients, histologically diseased resection margins in patients with IBD, preoperative albumin level lower than 3.5 g/dL, intraoperative blood loss of 200 mL or more, operative time of 200 minutes or longer, and intraoperative transfusion requirement were all identified as factors that increase risk of postoperative anastomotic dehiscence. Enteral nutritional optimization prior to elective surgery is essential. Proximal diversion should be considered for patients with all 3 intraoperative risk factors because these patients are at particularly high risk of anastomotic dehiscence. Pathologic specimen reports indicating histologic specimen margin involvement in patients with IBD should heighten physician awareness for possibility of postoperative AL.

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Author Contributions: Dr Telem had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Telem and Divino. Acquisition of data: Telem. Analysis and interpretation of data: Telem, Chin, Nguyen, and Divino. Drafting of the manuscript: Telem. Critical revision of the manuscript for important intellectual content: Chin, Nguyen, and Divino. Statistical analysis: Telem. Administrative, technical, and material support: Nguyen and Divino. Study supervision: Chin, Nguyen, and Divino.

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REFERENCES: None reported.

Seek Tricks for Leaks? No Answer in the Mix

In this useful publication, the Mount Sinai Hospital group refreshes our knowledge about anastomotic leaks (ALs) in colorectal surgery. The group pairs each patient with AL with 2 no-AL patients who underwent the same procedure with the same surgeon. The article reminds us of facts that have not changed much over the last 20 years: (1) the AL rate is 2.6%; (2) most ALs occur about 7 days after the operation; and (3) ileocolic anastomoses leak as frequently as colocolic anastomoses.

The article also offers excellent additional information based on a rigorous risk factor analysis: (1) a single preoperative factor (low albumin), 3 intraoperative factors (blood loss, blood transfusion, and long operation), and 1 histologic factor (involvement of specimen margins in IBD) increase the risk for AL; (2) the combination of the 3 intraoperative factors increases the risk by a lot; and (3) blood transfusion remains an independent predictor of AL in the presence of blood loss, which is also an independent predictor. Transfusion is not just a surrogate for blood loss but may alter the inflammatory cascade in ways that harm the patient, as other authors have also shown.

The limitations of this well-done study are multiple and raise serious doubts about the conclusions and recommendations:

1. The cutoff points used for the continuous values are completely arbitrary. Why are 200 mL of blood loss and 200 minutes of operation selected, other than they are easy to remember?

2. Comorbidities are assessed but not completely. It is hard to believe that they play no role. A description of severity and a Charlson comorbidity index are missing. The IBD incidence among patients with AL is 51%; among controls, 35%. This alone, even if not statistically significant owing to the small sample size, could account for the outcome difference.

3. The authors emphasize the intraoperative factors (which to a certain degree may be hard to change) but not the preoperative and histologic factors (which to a certain degree may be correctable).

4. The operative technique may be the most important factor. We all know that operative conditions are not always ideal. Tension, adhesions, and blood supply are factors that cannot be ignored and are not adequately described.

5. The severity of the leaks is not described either. I would prefer to have a small collection, easily drained by a percutaneous drain, any day over a colostomy requiring a second operation. There are “benign” leaks and lethal leaks. They cannot be lumped together.

6. Most importantly the recommendation to consider a colostomy in the presence of the 3 intraoperative factors is rather premature. It is based on only 11 patients who had all 3 factors. It is based on a 95% confidence interval that is almost unacceptably wide (2.8-175.4), indicating the low power of the study. Most importantly, it does not take into account the morbidity and mortality of colostomy and colostomy reversal.

There is no doubt that information from well-structured studies like this one bolsters our fund of knowledge and offers food for thought. But extrapolations about management are as hard as that colonic leak that will come despite your best effort.

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