Incidence and Risk Factors for Anastomotic Leakage in Colorectal Surgery: A Historical Cohort Study

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ABSTRACT: **Background:** Anastomotic leakage (AL) is a major complication following colorectal surgery, with many risk factors established to date. The incidence of AL varies in the medical literature and is dependent on research inclusion criteria and diagnostic criteria.

Objectives: To determine the incidence of and the potential risk factors for AL following colorectal surgery at a single academic medical center.

Methods: We retrospectively reviewed all operative reports of colorectal procedures that included bowel resection and primary bowel anastomosis performed at Sheba Medical Center during 2012. AL was defined according to the 1991 United Kingdom Surgical Infection Study Group criteria. Data were assessed for leak incidence within 30 days. In addition, 17 possible risk factors for leakage were analyzed. A literature review was conducted.

Results: This cohort study comprised 260 patients, and included 261 procedures performed during the study period. The overall leak rate was 8.4%. In a univariate analysis, male sex (odds ratio [OR] 3.37, 95% confidence interval [95%CI] 1.21–9.43), pulmonary disease (OR 3.99, 95%CI 1.49–10.73), current or past smoking (OR 2.93, 95%CI 1.21–7.10), and American Society of Anesthesiologist score ≥ 3 (OR 3.08, 95%CI 1.16–8.13) were associated with an increased risk for anastomotic leakage. In a multivariate analysis, male gender (OR 3.62, 95%CI 1.27–10.33) and pulmonary disease (OR 4.37, 95%CI 1.58–12.10) were associated with a greater risk.

Conclusions: The incidence of AL in the present study is similar to that found in comparable series. Respiratory co-morbidity and male sex were found to be the most significant risk factors.

IMAJ 2019; 21: 732–737

KEY WORDS: anastomotic leak (AL), anastomotic dehiscence, colorectal surgery, risk factors

Anastomotic leak (AL) is one of the most severe complications following colorectal surgery. It increases morbidity and mortality rates. It prolongs length of hospital stay, increases hospitalization costs, and may worsen patient oncologic outcome [1].

The reported incidence of AL in colorectal surgery is extremely diverse, ranging from 0.5% to 30% [2], and is largely dependent on the applied diagnosis criteria. Throughout the years, various authors used different definitions for AL such that the ability to compare between studies is limited. Bruce et al. [3], in a review from 2001, found 49 studies describing AL in colorectal surgery using 29 different definitions for lower gastrointestinal leakage [3]. Various groups have tried to create a uniform definition. In 1991 the United Kingdom Surgical Infection Study Group [4] proposed a definition, and in 2010 the International Study Group of Rectal Cancer (ISGRC) proposed their own definition and grading system for AL after rectal surgery [5]. Despite these attempts, a recent survey published in 2013 found that to date there is still significant heterogeneity in the definition of anastomotic leak among surgeons, and there is still no consensus [6]. Various publications have used routine screening tests, demonstrating subclinical leaks, and further complicating the debate whether subclinical leaks should be considered leaks as well, despite their unknown clinical significance.

In 2011, an attempt was made by the Israeli Ministry of Health to estimate national AL rates in patients undergoing colorectal resections [7]; however, the investigators did not publish their exact definition of AL, resulting in variability among participating centers. Our study aimed to measuring ALs according to pre-established criteria. This measurement, in turn, may be used as a basis for continuous improvement of quality of care.

In addition to the need for a unifying definition of AL, there is also a necessity for a leak severity classification system as AL ending in re-laparotomy or death should be viewed differently than AL treated with antibiotics or healing spontaneously. There have been attempts to create leakage severity scales [3,5] as well as more general attempts to classify the severity of surgical complications using the Clavien-Dindo surgical complication severity scale [8]. Despite these attempts, to date, there is no widely accepted complication severity score, which further complicates the optimal comparison of various publications.

In addition to the need for a unifying definition of AL, there is also a need for identification of the various risk factors contributing to its occurrence. Many potential patient- and disease-related risk factors have been investigated. Such risk factors include male gender, obesity, diabetes, hypertension, cardiovascular disease, pulmonary disease, smoking, renal disease, high American Society of Anesthesiologist's (ASA) score, malnutrition, radiation treatment, and various medications [9-13]. Surgery related risk factors include the type of resection and anastomosis, proper surgical technique, surgical duration, urgency, and blood transfusion [14-16]. While some risk factors are consistently described in the literature, others are controversial.

Anastomotic leak usually occurs within 30 days following surgery, although it has been shown that it may occur even later than that [17,18]. Consequently, AL can develop long after a patient has been discharged from the hospital, and may be harder to detect due to the less severe presentation.

The aim of this study was to evaluate the AL rate in one academic medical center compared to other institutions as described in the literature and to identify risk factors for AL at our institution.

PATIENTS AND METHODS

We conducted a review of the literature to estimate what comparable leakage rates are. The following PubMed search terms were used to find relevant publications: ("national"[Title] OR "nation"[Title] OR "multicentre"[Title] OR "nationwide"[title]) AND ("anastomotic leak"[Title] OR "anastomotic leakage"[Title] OR "anastomotic dehiscence"[Title]). The search yielded 11 publications of which 6 were selected. Excluded from the table were publications with n ≤ 1000, and duplicate publications by the same author using the same database (in this case the publication with the largest number of participants) was included.

Sheba Medical Center is a public 1900-bed general, acute care, and rehabilitation hospital affiliated with Tel Aviv University. Data was retrospectively collected from the electronic medical records of all colorectal procedures performed at Sheba Medical Center during the year 2012. Relevant procedures were identified according to the ICD9 coding system. Excluded were procedures without an anastomosis, with a small bowel to small bowel anastomosis, re-operation within 30 days, duplicates, and patients younger than 18 years of age.

Anastomotic leak was defined based on the 1991 United Kingdom Surgical Infection Study Group as "leak of luminal contents from a surgical join between two hollow viscera" and diagnosed radiologically by a radiographic enema with hydrosoluble contrast or by computed tomography (CT) with presence of intra-abdominal collection adjacent to the anastomosis, or evidence of extravasation of contrast material; clinically with evidence of extravasation of bowel contents or gas through a wound or drain; by endoscopy; or intraoperatively. Routine imaging was not performed and only patients who showed clinical symptoms following surgery (e.g., fever, leukocytosis, peritonitis) underwent further investigation. The study was approved by the hospital ethics committee in agreement with the Helsinki Declaration.

Data collected included parameters relating to patient characteristics, surgery indication, surgical data, and postoperative complications. The information is detailed in Table 1 and Table 2. Postoperative complications were recorded within 30 days of procedure and classified according to the Clavien-Dindo surgical complications severity scale.

STATISTICAL ANALYSIS

Descriptive statistics were summarized as means, standard deviations, medians, and ranges for the continuous variables and as frequencies for the categorical variables using R statis-

Table 1. Characteristics of procedures performed (total of 261 cases)

Gender	
Female, n	124 (47.5%)
Male, n	137 (52.5%)
Age, years	
Mean ± SD	63.1 ± 15.4
Range	19–96
Median	65
Body mass index, kg/m2	
Mean ± SD	26.2 ± 4.9
Median	25
Range	15–53
American Society of Anesthesiologists Score	
Mean ± SD	2.5 ± 0.6
ASA 3 or above	127 (48.7%)
Surgery indication	
Neoplasm	211 (80.8%)
Inflammatory bowel disease	19 (7.2%)
Diverticular disease	9 (3.4%)
Closure of colostomy	11 (4.2%)
Other	11 (4.2%)
Urgency	
Elective	247 (94.6%)
Urgent	14 (5.4%)
Approach	
Open	125 (48.1%)
Laparoscopic	135 (51.9%)
Operating duration, in minutes	
Mean ± SD	203.8 ± 96.8
Median and range	180 ± 35-675
Type of anastomosis	
Ileum to right colon	102 (40.2%)
Ileum to left colon	23 (9.1%)
Colo-colic	24 (9.4%)
Colon: upper rectum	42 (16.5%)
Colon: mid rectum	31 (12.2%)
Colon: low rectum	32 (12.6%)
Leak	
No	239 (91.6%)
Yes	22 (8.4%)

Characteristics in this table are according to the number of procedures. One patient's characteristics were counted twice as he underwent two separate procedures

SD = standard deviation

tical software. Differences in independent variables between patients who developed a leak and patients who did not were examined using the Chi-square test (or Fisher's exact test when necessary) for categorical variables. Continuous variables were evaluated by *t*-tests or the Kruskal-Wallis non-parametric test. For the purpose of statistical analysis, the anastomosis type variable was regrouped.

$P \leq 0.05$ was considered statistically significant. Univariate and multivariate logistic regression modeling techniques were used to identify risk factors for anastomotic leak. Odds ratios (OR) with 95% confidence intervals (95%CI) were reported in addition to the *P* values from the logistic regression modeling.

RESULTS

Our computerized data search retrieved 356 colorectal resections performed during 2012 in 355 patients. After review of all medical records, 95 patients were excluded from the study (70 did not undergo a procedure with anastomosis, 22 had a small bowel to small bowel anastomosis, 2 were double listed, and 1 had a second surgery within 30 days due to a complication), thus leaving for analysis 261 procedures performed in 260 patients.

The characteristics of the patients and procedures in this series are summarized in Table 1. Of the patients who underwent rectal resection, 17/63 patients underwent radiation therapy. Furthermore, proximal diversion was constructed in 6.4% of the colon to midrectum anastomoses (2/31) and in 71% of the lower rectum anastomoses (23/32). For the purpose of statistical analysis, the anastomosis type variables were regrouped into three larger groups (right colon/left colon/rectal resections). Two surgeries involved more than one anastomosis and were excluded from the relevant statistical analysis.

The overall anastomotic leak rate was 8.4% (22/261). Of the 22 leak cases, 11 were diagnosed using contrast CT, which showed a collection adjacent to the anastomotic site. Two were diagnosed by contrast extravasation on CT, three were diagnosed with fecal content in wound or drain, and six during re-laporotomy.

Of the 22 leaks, 10 were treated with antibiotics without surgical intervention (Clavien-Dindo grade 2), 4 underwent percutaneous drainage of an abscess (Clavien-Dindo grade 3a), and 8 were treated by surgical intervention (Clavien-Dindo grade 3b). There was a single case of mortality in the leak group (Clavien-Dindo grade 5). One patient in our series underwent two unrelated colon resections during 2012 and presented with leak complications in both procedures. The mortality rate in the AL group was 4.5% compared to 0.4% in the general group. The average length of hospitalization was 7.4 ± 4.7 days in the non-leak group and 20.2 ± 17 days in the leak group. The mean time to leak diagnosis was 8.8 ± 5.3 days after surgery.

The highest rate of leakage was in anastomosis between the ileum to the left colon in extended right colectomy or subtotal colectomy with a leak incidence rate of 26% (5/23). The second highest AL rate was in anastomosis between the colon to lower rectum following low anterior resection with a leak rate of 15.6% (5/32).

In a univariate analysis [Table 2] the following parameters were associated with an increased risk for anastomotic leakage: male sex: OR 3.37, 95%CI 1.21–9.43; respiratory co-morbidity: OR 3.99, 95%CI 1.49–10.73; current or past smoking: OR 2.93, 95%CI 1.21–7.10; and ASA score ≥ 3: OR 3.08, 95%CI 1.16–8.13. Significant variables were entered into multivariate models, but due to high correlations among the variables (2–4), the best multivariate models contained only one of these variables together with the gender variable. The best of these models showed male gender (OR 3.62, 95%CI 1.2–10.33) and pulmonary disease (OR 4.37, 95%CI 1.58–12.10) to be the variables associated with the greatest risk.

Our review of the literature regarding AL rates in other national series [Table 3] showed that AL rates vary between 3.8%–11.6%, and are largely influenced by the resection and anastomosis type included in the series, as well as the definition of AL.

DISCUSSION

In this retrospective review of 261 colorectal resection procedures, we found the leak rate following colorectal anastomosis to be 8.43%. Male sex, ASA score of 3 and above, history of smoking, and pulmonary co-morbidity were all associated with an increased risk for AL. The primary objective of our study was to assess the overall leak rate at Sheba Medical Center, compared with other medical centers as described in the literature.

The lack of a uniform definition for AL makes the comparison of AL rates among various studies challenging. Specifically, it is not clear whether finding of a fluid collection adjacent to the anastomosis in a CT scan should be interpreted as an AL regardless of contrast material in the collection (an issue that is further complicated by the decreasing threshold for performing CT scans during the early postoperative course). In addition, studies tend to include a different subset of patients as well as procedures, which only add to this complexity.

Our attempt to compare our leakage rates to those at other medical centers [Table 3] shows that in similar studies AL rates vary between 3.8–11.6%, and are largely influenced by resection and anastomosis type, as well as the definition of AL. Publications that define AL as leaks requiring intervention [19] (equivalent to Clavien-Dindo grade 3 or higher) will naturally have a lower AL rate compared to studies that also include AL diagnosed by imaging only and treated with antibiotics with no surgical, endoscopic, or radiological intervention [19,20]. In addition, studies that focus on rectal surgery [21,22] usually present higher leakage rates (as low colorectal anastomoses are associated with higher leakage rates). Although many quote a general acceptable leak rate of 3–6%, it seems that these figures

Table 2. Univariate analysis of risk factors for anastomotic leakage

	No leak (n=239, 91.57%)	Leak (n=22, 8.43%)	*P* value
Age, years			
Mean ± SD	62.70 ± 15.42	67.86 ± 14.15	0.132
‹ 75	184 (77.0)	14 (63.6)	0.254
≥ 75	55 (23.0)	8 (36.4)	
Gender			
Male	120 (50.2)	17 (77.3)	
Female	119 (49.8)	5 (22.7)	**0.027**
Surgery indication			
Neoplasm	195 (81.6)	16 (72.7)	0.185
Diverticular disease	9 (3.8)	0 (0.0)	
Inflammatory bowel disease	17 (7.1)	2 (9.1)	
Other benign	10 (4.2)	1 (4.5)	
Closure of stoma	8 (3.3)	3 (13.6)	
Hypertension			
No	126 (52.7)	9 (40.9)	0.402
Yes	113 (47.3)	13 (59.1)	
Cardiovascular disease			
No	192 (80.3)	15 (68.2)	0.284
Yes	47 (19.7)	7 (31.8)	
Diabetes mellitus			
No	185 (77.4)	15 (68.2)	0.475
Yes	54 (22.6)	7 (31.8)	
Respiratory disease			
No	214 (89.5)	15 (68.2)	**0.010**
Yes	25 (10.5)	7 (31.8)	
Renal disease			
No	218 (91.2)	19 (90.5)	1.000
Yes	21 (8.8)	2 (9.5)	
Smoking history (current or past)			
No	166 (70.9)	10 (45.5)	**0.026**
Yes	68 (29.1)	12 (54.5)	
Blood transfusion			
No	210 (88.2)	17 (77.3)	0.253
Yes	28 (11.8)	5 (22.7)	
American Society of Anesthesiologists score			
< 3	128 (53.6)	6 (27.3)	**0.033**
≥ 3	111 (46.4)	16 (72.7)	
Body mass index, kg/m²			
< 30	191 (80.3)	21 (95.5)	0.141
≥ 30	47 (19.7)	1 (4.5)	
Surgery duration			
< 3 hours	116 (48.7)	8 (36.4)	0.374
≥ 3 hours	122 (51.3)	14 (63.6)	
Approach			
Open surgery	112 (47.1)	13 (59.1)	0.391
Laparoscopic surgery	126 (52.9)	9 (40.9)	
Timing			
Elective surgery	228 (95.4)	19 (86.4)	0.192
Emergency surgery	11 (4.6)	3 (13.6)	
Type of resection			
Right colectomy	114 (48.9)	11 (52.4)	0.131
Left colectomy	64 (27.5)	2 (9.5)	
Rectal surgery	55 (23.6)	8 (38.1)	
Proximal diversion (of rectal resections)			
No	35 (64.8)	2 (25.0)	0.079
Yes	19 (35.2)	6 (75.0)	

Bold indicates significance
SD = standard deviation

are usually based on a rather narrow definition of anastomotic leak and thus are underestimations. AL in our study was defined according to the United Kingdom Surgical Infection Study Group criteria considering a fluid collection adjacent to the anastomosis as an AL. This definition can explain the higher rate of AL found in our study; nonetheless, our results are consistent with other studies using the same criteria. Frasson et al. [23] showed a leak rate of 8.7% in a national multicenter trial prospectively evaluating 3193 patients, using United Kingdom Surgical Infection Study Group criteria as well. Although the leakage definition used in both studies is similar, there are differences that should be noted. In their multicenter study, Frasson et al. included only cancer patients with tumors located 15 cm from the anal verge or higher, excluding patients with low rectal anastomoses. We included low rectal anastomoses as well, which poses a higher risk for AL. However, we collected only 30-days leak rate, while Frasson's group looked 60-days leak rate.

As previous studies have shown [17,18] anastomotic leaks may occasionally present later than 30 days; hence, our search for leaks within 30 days may have excluded additional leaks that developed later. Furthermore, in their study, Frasson et al. included patients that underwent emergency surgery, as well as patients in whom primary anastomosis with no protective stoma was conducted. These two factors usually contribute to higher rates of anastomotic leak that are expressed clinically. Had we chosen a narrower definition for AL, such as a leak requiring intervention other than medication, our leak rates would have been 4.6%, similar to other studies with a narrower definition for AL [21]. Importantly, we did not hold routine contrast examinations, and only patients with clinical signs suggesting anastomotic leak underwent imaging studies; hence, we may have missed some subclinical anastomotic leaks that would have been noted had all patients undergone radiological screening.

Four risk factors were found to be of significance on univariate analysis: male sex, high ASA score, smoking, and pulmonary disease. These factors have also been found to be risk factors for AL in other studies. Many publications have shown an association between male sex and higher leakage rates, especially those involving low rectal anastomosis. The narrower male pelvis has been suggested as the cause for this, as it complicates the surgical procedures [9.11]. In our study male sex was found to be a strong predicting factor for AL in a mutivariate analysis as well. Various authors have shown that current smoking and a history of past heavy smoking have been associated with higher rates of AL [11]. One explanation for this finding is that smoking may cause microvascular disease, which leads to ischemia and increases the risk of leakage [9].

A weakness in our research is that we did not quantify the smoking history of every smoker, and having done so may have led to more significant results. In addition, we did not distinguish between active and past smokers, which were grouped as one, and a separation into two groups may have yielded better

Table 3. Anastomotic leakage rates in large series factoring leak definition and surgeries included

Authors	Leak rate	N	Leak definition	Surgeries included
Frasson et al. [23]	8.7%	3193	AL was defined as "leak of luminal contents from a surgical join between 2 hollow viscera" diagnosed (1) radiologically, by a radiographic enema with hydrosoluble contrast or by CT with presence of intra-abdominal collection adjacent to the anastomosis; (2) clinically, with evidence of extravasation of bowel content or gas through a wound or drain; (3) by endoscopy; or (4) intraoperatively	Colon surgery Leak within 60 days
Krarup et al. [19]	6.4%	9333	AL was defined according to the guidelines of the DCCG: "Clinical symptoms suggesting AL and confirmed by contrast enema or CT scan" Patients with AL were identified in the DCCG database or in the Danish Patient Register using the International Classification of Disease (ICD-10) for diagnosis and reoperation codes associated with AL (DT813A, KJWF00)	Colon surgery
Eriksen et al. [21]	11.6%	1958	Anastomotic leakage was defined by clinical criteria: pelvic abscess, fecal discharge from wound, septicemia, peritonitis, with or without radiologically confirmed leakage	Mesorectal excisions for rectal cancer
Midura et. al. [20]	3.8%	13684	Anastomotic leak was defined as minor leak requiring percutaneous intervention or major leak requiring laparotomy	Colonic resections included. Anterior resection included. Rectal cancer resections not included
Bakker et al. [14]	7.5%	15,667	Anastomotic leakage was defined as clinically relevant leakage requiring surgical or radiological re-intervention	Colon surgery
den Dulk, M. et al [22]	9.7%	2726	Anastomotic leakage was defined as clinically apparent leakage such as fecal discharge from pelvic drain or abdominal wound, or radiologically, endoscopically or surgically proven anastomotic leakage in symptomatic patients such as those with peritonitis	Rectal surgery

AL = anastomotic leakage, CT = computed tomography

results. A high ASA score has also been found to have a correlation with increased anastomotic leak incidence [12], and is a better AL predictor than the Charlson Comorbidity Index [11]. Nonetheless, as the ASA score is very general and includes in its calculation many known risk factors for AL, it cannot be used to explain the increased risk, rather it can serve as a general prediction tool. Pulmonary disease has been found to be a risk factor for AL in various studies [24,25]. However, patients with pulmonary disease many times receive corticosteroid treatment, and as corticosteroids have also been shown to increase AL risk [12,24,25], one must be aware that they may serve as a possible confounding factor in this case.

Age, surgery indication, and laparoscopic surgery were not found to be significant risk factors. This finding is in accordance with other studies, although with regard to surgery indication it is difficult to reach a meaningful conclusion due to the small size of the groups. Other risk factors that have been shown to be of significance in other series were not found in our study, possibly due to the heterogeneous group of patients included in this study. These risk factors include: diabetes, hypertension, cardiovascular disease, renal disease, blood transfusion, obesity, long surgery duration, urgent surgery, rectal surgery, and proximal diversion. In contrast to studies that showed emergent surgery as a risk factor [14], surgical urgency was not found as a significant risk factor for AL in our study. Possible explanations are the small sample size and selection bias. We do not know how many patients in the urgent setup did not have AL since they were excluded. It is reasonable to believe that only patients with favorable conditions were restored, therefore serving as a favorable selection bias. Rectal surgery was not found as a significant risk factor for AL in our study, in contrast to the known and well established data. A possible explanation is the high diversion rate (39.6%). It has been demonstrated in the past that proximal diversion doesn't decrease leakage rate but rather may diminish the clinical sequelae of a leak. With a diversion rate of 39.6% some of the AL could have been undetected.

We found smoking to be a significant risk factor for AL. This finding is of great significance as it is one of the few risk factors that can actively be modified. Patient education on the potential dangers of smoking should be emphasized, and patients should be actively encouraged to quit smoking prior to elective procedures.

Other limitations of the study include its retrospective nature and possible data retrieval errors that could have occurred as a consequence. In addition, there may have been loss to follow-up due to referral to other medical centers. Nevertheless, we expect this loss to be negligible as patients tend to return to their surgeon in the event of a complication.

Now that a clear working definition of AL has been set, it is our aim to expand this study to an ongoing registry based on automatic extraction of data from electronic medical charts. An ongoing registry will allow us to assess the efficacy of intervention such as cessation of smoking and other interventions aimed at reducing AL rate and will contribute to the ongoing research and efforts to reduce AL incidence.

CONCLUSIONS

The incidence of AL varies greatly throughout medical literature. The overall AL rate in our study was 8.4%, (of which 4.6% required intervention). Significant independent risk factors for AL were male sex and pulmonary co-morbidity. The importance of this study is its being the first measurement of the actual AL rates in the Sheba Medical Center. The definition set here could serve as a basis for a National Registry that will set at benchmark among medical centers and will help reduce morbidity and mortality following surgical care.

Acknowledgements

We dedicate this article to our dear colleague, Dr. Ron Shapiro, who so passionately worked on this research, and who is not here with us today to enjoy the fruits of his work. May his memory be blessed.

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Capsule

Microbiota can direct immune cell development and subsequent function at mucosal sites

Mucosal-associated invariant T (MAIT) cells play an important role in mucosal homeostasis. MAIT cells recognize microbial small molecules presented by the major histocompatibility complex class Ib molecule MR1. MAIT cells are absent in germ-free mice, and the mechanisms by which microbiota control MAIT cell development are unknown. **Legoux** and co-authors showed that, in mice, development of MAIT cells within the thymus is governed by the bacterial product 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil, which rapidly traffics from the mucosa to the thymus, where it is captured by MR1 and presented to developing MAIT cells. **Constantinides** et al. reported that MAIT cell induction only occurs during a limited, early-life window and requires exposure to defined microbes that produce riboflavin derivatives. Continual interactions between MAIT cells and commensals in the skin modulates tissue repair functions. Together, these papers highlight how the microbiota can direct immune cell development and subsequent function at mucosal sites by secreting compounds that act like self-antigens.

Science 2019; 366: 494.eaax6624
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"If you're not failing every now and again, it's a sign you're not doing anything very innovative"

Woody Allen (born 1935), American movie director and actor.