Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection

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Abstract

AIM: To analyze the time interval ('delay') between the first occurrence of clinical parameters associated with anastomotic leakage after colorectal resection and subsequent relaparotomy.

METHODS: In 36 out of 289 consecutive patients with colorectal anastomosis, leakage was confirmed at relaparotomy. The medical records of these patients were retrospectively analysed and type and time of appearance of clinical parameters suggestive of anastomotic leakage were recorded. These parameters included heart rate, body temperature, local or generalized peritoneal reaction, leucocytosis, ileus and delayed gastric emptying. Factors influencing delay of relaparotomy and consequences of delayed recognition and treatment were determined.

RESULTS: First documentation of at least one of the predefined parameters for anastomotic leakage was after a median interval of 4 ± 1.7 d after the operation. The median number of days between first parameter(s) associated with leakage and relaparotomy was 3.5 ± 5.7 d. The time interval between the first signs of leakage and relaparotomy was significantly longer when a weekend was included (4.2 d vs 2.4 d, P = 0.021) or radiological evaluation proved to be false-negative (8.1 d vs 3.5 d, P = 0.007). No significant association between delay and number of additional relaparotomies, hospital stay or mortality could be demonstrated.

CONCLUSION: An intervening weekend and negative diagnostic imaging reports may contribute to a delay in diagnosis and relaparotomy for anastomotic leakage. That delay was more than two days in two-thirds of the patients.

INTRODUCTION

Anastomotic leakage after colorectal resection is an adverse event with a tremendous impact on morbidity, mortality and quality of life. Mortality rates of more than 30% in patients who developed anastomotic leakage have been reported in the literature[1-6]. Clinically symptomatic leakage often requires one or more operative reinterventions with frequent need for intensive care admission and prolonged hospital stay. When a stoma is constructed at reexploration, this is meant to be temporary but often appears to be permanent. In those patients whose bowel continuity is restored, late functional consequences may be encountered[7].

Many studies have concentrated on risk factors for anastomotic leakage, including comorbidity and surgical technique, trying to find ways to prevent leakage in high-risk groups[2,4,6,8-11]. When leakage occurs, it seems important to detect this complication at an early moment to minimize associated morbidity and mortality[12]. However, the clinical diagnosis of anastomotic leakage is often difficult and it may only become evident after several days of close observation[13]. Little is known about the incidence and consequences of a delay in the diagnosis and subsequent treatment of anastomotic leakage after colorectal resection. Therefore, we retrospectively determined time intervals between first clinical signs and relaparotomy and assessed risk factors and consequences of a delay in recognition and treatment of anastomotic leakage.

MATERIALS AND METHODS

Between January 2000 and July 2003, 289 consecutive patients underwent an ileocolic, colo-colonic or colorectal

anastomosis at the Sint Lucas Andreas Hospital, a non-university teaching hospital in Amsterdam, the Netherlands. There were 158 females and 131 males with a mean age of 69 (range 20-96) years. In 15 patients (5%), the anastomosis was performed to restore colonic continuity after previous colostomy, while in the remaining patients the anastomosis was constructed immediately following bowel resection. Ileocolonic resection was performed in 27 patients (9%), right hemicolectomy in 94 (33%), transverse colonic resection in 10 (3%), left hemicolectomy in 20 (7%), sigmoidal resection in 72 (25%) and subtotal or total colectomy in 7 patients (3%). A low anterior resection was performed in 44 patients (15%). Patients electively planned for colonic or rectal resection were admitted to the hospital one day before surgery. Bowel preparation was given to patients undergoing left-sided resections and consisted of oral phosphate solution. In addition, one enema was given the morning of surgery to patients who underwent low anterior resection. Antibiotic prophylaxis consisted of a cephalosporin and metronidazol and was given in a single dose during induction of anesthesia. Operations were performed by consultant surgeons in 184 patients (64%) and by trainees under supervision in 105 patients (36%). Type of anastomosis (e.g. end-to-end or end-to-side) depended on the preference of the individual surgeon. Hand-sewn anastomoses were performed using a one layer continuous suture of propylene 3/0 in 209 patients. Stapled anastomoses were performed in 80 patients (28%). Postoperative oral intake was gradually restarted depending on nausea, bowel movements, gastric tube production (if applied), and passage of flatus or stools. No fast-track recovery programs were used during the study period. Patient's temperature, blood pressure, and heart rate were routinely recorded three times daily. The patients were seen by the attending doctor at least once daily during morning rounds, even during the weekends. Radiological examination of the anastomosis by contrast radiography or computed tomography (CT) was not performed on a routine basis, but only when leakage was suspected on clinical grounds.

For the purpose of this study, simple clinical parameters suggestive of anastomotic leakage were identified from the literature[1,14,15] and retrospectively collected from the records of patients who developed anastomotic leakage confirmed at relaparotomy. These parameters included tachycardia (heart rate > 100 beats per minute), fever (body temperature > 38℃), local or generalized peritoneal reaction during physical examination, leucocytosis (> 10×10^3/mL), prolonged adynamic ileus (> 2 d) as demonstrated by symptoms and signs during physical examination or plane abdominal radiography, and delayed gastric emptying (increased gastric tube production of more than 200 mL per day or vomiting necessitating tube reinsertion). In addition, the postoperative day of first appearance of any of these parameters was scored, as well as the first day the attending doctor recognized these signs, resulting in a description in the patient's files. Delay until relaparotomy was calculated from the day of first retrospective presence of clinical parameters associated with leakage and from the day the possibility of anastomotic leakage was explicitly suggested in the

Table 1   Patient and treatment characteristics of 36 patients with anastomotic leakage confirmed by relaparotomy

Characteristic	n (%)
Gender	
Male	21 (58)
Female	15 (42)
Mean age (range) (yr)	67 (26-87)
Mean Quetelet index (range)	25 (17-43)
American Society of Anesthesiology score	
1	14 (39)
2	16 (44)
3	6 (17)
Comorbidity	
Laparotomy in medical history	14 (39)
Diabetes mellitus	6 (17)
Cardiovascular disease	17 (47)
Preoperative radiotherapy	4 (11)
Chronic Obstructive Pulmonary Disease	8 (22)
Type of operation	
Ileocolonic resection	5 (14)
Right hemicolectomy	3 (8)
Transverse colonic resection	2 (6)
Left hemicolectomy	1 (3)
Sigmoidal resection	14 (39)
Subtotal colectomy	3 (8)
Anterior resection	7 (19)
Restoring continuity after colostomy	1 (3)

medical records by the attending doctor. The following factors were tested for their association with delay of relaparotomy for anastomotic leakage: age, sex, body mass index, site of anastomosis, radiological examination, and presence of a weekend in the period between first appearance of clinical parameter(s) and relaparotomy. To determine the influence of a weekend on the delay of relaparotomy, patients with a delay of more than seven days were excluded. Consequences of a delay for number of relaparotomies, hospital stay, and in-hospital mortality were assessed.

Statistical analysis

Univariate analyses using the Mann-Whitney test, F test and χ^2-test were performed to compare data of two groups. Spearman's correlation coefficient was used to determine the correlation between two continuous variables. Significance was set at $P \leqslant 0.05$ (two-sided). Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS, Chicago, IL, USA).

RESULTS

Anastomotic leakage was confirmed during relaparotomy in 36 patients. Patient and treatment characteristics of the 36 patients are displayed in Table 1. Symptomatic anastomotic leakage occurred despite the presence of a diverting ileostomy in three patients after low anterior resection. In three patients, anastomotic leakage was not confirmed during first relaparotomy, but only after repeated laparotomy at three ('second look' at day one, 'third look' at day three), 24 and 28 d after the initial operation, respectively. Apart from irrigation of the contaminated abdominal cavity, the operative procedure for leakage consisted of breakdown of the anastomosis

Table 2 Incidence and median postoperative day of first occurrence of simple clinical parameters in 36 patients with anastomotic leakage confirmed at relaparotomy

Variable	Incidence (%)	Median postoperative day (SD)
Tachycardia (> 100 beats/min)	61	4 (2.6)
Fever (> 38℃)	67	5 (2.4)
Peritoneal reaction	28	6 (3.7)
Leucocytosis (> 10 × 10³/mL)	72	6 (2.5)
Adynamic ileus	47	6 (4.6)
Delayed gastric emptying	67	4 (2.0)

SD: standard deviation.

Table 3 Median time intervals between first occurrence of clinical parameters or the attending doctor's suggestion of anastomotic leakage in the medical record and relaparotomy

Signs/symptoms First occurrence of:	Median delay of relaparotomy (d)	SD	Range
Tachycardia	2.0	7.2	0-29
Fever	2.8	5.7	0-29
Peritoneal reaction	0.8	2.8	0-8
Leucocytosis	2.0	6.1	0-29
Ileus	1.5	2.4	0-9
Delayed gastric emptying	2.0	5.2	0-25
At least one parameter	3.5	5.7	0-29
At least two parameters	2.5	5.4	0-12
At least three parameters	1.8	5.7	0-8
Doctor's suggestion of leakage in medical record	1.0	5.1	0-29

Table 4 Risk factors for prolonged delay of relaparotomy because of anastomotic leakage

Variable		*n*	Mean delay (d)	*P*
Age (yr)	< 70	19	4.5	0.71
	≥ 70	17	4.9	
Sex	Male	21	4.5	0.95
	Female	15	4.9	
Body mass index (kg/m²)	< 25	18¹	4.6	0.29
	≥ 25	14	5.3	
Site of anastomosis	Left	25	4.8	0.29
	Right	11	4.3	
Radiological examination performed	Yes	21	6.0	0.051
	No	15	2.7	
Outcome of radiological examination	FN	9	8.1	0.007
	TP/NP	27	3.5	
Weekend included in period between first clinical parameter and relaparotomy	Yes	14²	4.2	0.021
	No	18	2.4	

FN: false-negative; TP: true-positive; NP: not performed. ¹Four missing values, ²Four patients excluded with delay of more than seven days. Significance of differences in delay between subgroups is determined using the Mann-Whitney test.

and construction of a colostomy in 21 patients (58%), a diverting loop-ileostomy in twelve (33%), abscess drainage in two (6%) and no additional intervention in one patient (3%).

For the 36 patients with leakage confirmed at relaparotomy, the incidence and median postoperative day of first occurrence of the simple clinical parameters are displayed in Table 2. The first appearance of at least one of these signs was after a median interval of 4 (± 1.7; range 1-8) d after the operation. This interval was 5 ± 2.3 (range 2-12) d and 5.5 ± 2.8 (range 2-12) d for at least two and three signs, respectively. Relaparotomy for anastomotic leakage was performed after a median interval of 7 d after initial surgery (± 4.1; range 3-24) d. The median number of days between the first occurrence of each specific parameter, at least one parameter, at least two parameters and at least three parameters associated with leakage and relaparotomy are displayed in Table 3. The median time interval between the presence of at least one positive parameter and relaparotomy ('the delay') was 3.5 d; 23 relaparotomies for anastomotic leakage (64%) were performed after a delay of more than two days. The median number of days between the attending doctor's suggestion of anastomotic leakage in the medical records and relaparotomy was one day.

A negative result of either contrast study or CT scanning in nine patients resulted in a significantly longer delay of relaparotomy as shown in Table 4. If a weekend (Saturday and/or Sunday) was included in the time interval between the first positive parameter suggestive of leakage and relaparotomy, delay of relaparotomy was also significantly longer in comparison with patients in whom observation and decision to reoperate did not take place during a weekend. No other factors determining the length of the delay could be demonstrated (Table 4).

After the first relaparotomy for anastomotic leakage, one additional laparotomy was performed in eight patients (22%) and more than one relaparotomy in another 10 patients (28%). Although the patients who needed at least one additional relaparotomy did have a longer delay between the first appearance of a clinical parameter and the first relaparotomy in comparison with patients who did not need additional relaparotomies [6.0 (± 7.6) d *vs* 3.3 (± 2.4) d], this difference did not reach statistical significance (*P* = 0.52). Patients with anastomotic leakage were admitted to the hospital for a mean period of 59 (range 7-259) d. There was no significant correlation between the delay of relaparotomy and duration of hospital stay (Spearman's correlation coefficient 0.16, *P* = 0.34). Overall in-hospital mortality was 36% (13 of 36 patients). Delay of relaparotomy for anastomotic leakage was not significantly longer in patients who died postoperatively (5.5 ± 5.6 d *vs* 4.2 ± 5.8 d for patients who did not have a delay, *P* = 0.54).

DISCUSSION

Two thirds of relaparotomies were performed more than two days from the first appearance of at least one positive parameter suggestive of anastomotic leakage with a median delay of 3.5 d. This is similar to the median delay of 4 d in a series of 22 patients with clinical symptomatic leakage as reported by Sutton *et al*[13]. Even if at least three positive parameters were present, it took a median number of 1.8 d until relaparotomy for anastomotic leakage was performed in our series. In a study by Alves *et al*[14], the risk of leakage increased to 67% if three or more signs associated with anastomotic failure were present. A remarkable finding

was the increase in delay when signs and symptoms suggestive of leakage appeared just before or during a weekend. During weekends, all patients are seen by a staff surgeon and a surgical resident during morning rounds on Saturday as well as on Sunday. The higher work load, the absence of the attending surgeon who initially performed the anastomosis, and the absence of a plenary discussion of clinical problems by the entire surgical staff during weekends may explain this disturbing finding.

The routine use of radiographic imaging in diagnosing anastomotic leakage is surrounded by controversies. We found that a negative result of either contrast study or CT scanning in nine patients resulted in a significantly longer delay of relaparotomy. This observation opens the discussion whether to perform radiographic imaging before relaparotomy. Nicksa et al[16] retrospectively studied 36 patients who were reoperated for anastomotic leakage and found that 3 of the 18 contrast enemas (17%) and 14 of the 27 CT scans (52%) were false-negative. Another study described 16 patients with a clinical anastomotic leakage, in whom four imaging studies (25%) were initially misinterpreted[17]. A similar sensitivity was reported by Akyol et al in a series of 233 patients who underwent left sided colonic or colorectal anastomoses. The false-negative percentage of a routine water soluble contrast enema in the early postoperative period was 22% (11 of 51 patients with anastomotic leakage)[18]. None of these studies describe the impact of imaging on the delay of relaparotomy.

But what does eventually lead to the decision to perform a relaparotomy? Is it one specific parameter that has more impact than some others or is it a specific combination of positive parameters? Comparing the delay after each individual parameter, the presence of peritoneal reaction is the only parameter that resulted in surgical intervention within 24 h in most cases. It is unclear whether this symptom is so important in surgical decision making or it is just a relatively late sign which in combination with other earlier positive parameters makes relaparotomy inevitable. The difficulty in clinical decision making is calculating the pre-test chance of an event (i.e. anastomotic leakage) based on a number of predictive factors. In addition, a cut-off point has to be determined at which the optimum is reached in terms of benefit of an intervention on the one hand and unnecessary harm on the other. It would seem that watchful waiting as long as it is not associated with significant morbidity and mortality would be preferable to early re-laparotomy and a higher negative re-exploration rate. The question is at what point the morbidity of waiting outweighs the morbidity of operating. Known risk factors, such as the level of anastomosis, chronic obstructive pulmonary disease, obesity, the use of steroids, poor nutritional state or the need for blood transfusion increase the chance of anastomotic leakage beforehand[2,4,6,9,10]. The finding of adynamic ileus, fever or leucocytosis in high-risk patients will further increase the pre-test chance and may facilitate the decision to reoperate in these patients. However, one should take into account the risk of false-positivity of these clinical parameters which may result in a false-negative reintervention. The complete diagnostic evaluation of the clinical parameters identified from the literature

(including sensitivity, specificity and positive/negative predictive value) was beyond the scope of the present study. In the previously mentioned study by Alves et al[14], clinical parameters suggestive of anastomotic leakage were analyzed in 655 patients who underwent colorectal resection. They found a significantly higher number of patients with fever on day two, absence of bowel action on day four, diarrhea before day seven, collection of more than 400 mL of fluid through abdominal drains from day zero to three, renal failure on day three and leucocytosis after day seven in the group in which anastomotic leakage occurred compared with the uncomplicated group. No other studies on the incidence and timing of these signs and symptoms have been published to our knowledge. Ultimately, a prospective analysis should be performed of all known risk factors and clinical parameters in order to construct a decision model that can help the surgeon to make a weighed choice for the individual patient.

What can minimize the delay in diagnosis and treatment of anastomotic leakage besides simple clinical parameters? Radiological examination of the anastomosis can be misleading[19]. Negative contrast studies and/or CT scanning undoubtedly result in a longer delay before surgical reintervention. Currently, we prospectively collect data about the additional value of radiological imaging of the anastomosis. A few investigational studies have focused on biochemical analysis of effluents of abdominal drains in patients who underwent colorectal anastomosis. Positive correlations with anastomotic leakage were found for lysozyme activity level and endotoxins[20,21]. The value of these findings in daily clinical practice, however, is probably limited.

The finding that patients who ultimately died in the hospital did not have had a longer delay of relaparotomy is comparable with observations that were done by Alves et al[14]. In that study, a non-significantly higher mortality rate was seen in patients who were reoperated on or after day five compared to those reoperated before day five. The absence of a significant association between delay of relaparotomy for anastomotic leakage and mortality is probably just a reflection of the small number of patients in both studies. It is our opinion that delay of relaparotomy in a patient with peritonitis should have an impact on outcome and that a more aggressive approach probably reduces morbidity and mortality.

In conclusion, although positive clinical parameters associated with anastomotic leakage were observed relatively early in the postoperative period, the final decision to perform a relaparotomy took a median of 3.5 extra days. The surgical team must be vigilant in the clinical observation of patients in the immediate postoperative period, also on weekends and review carefully the interpretation of diagnostic imaging of the anastomosis. Especially patients at an increased risk of anastomotic leakage due to comorbidity, septic conditions, technical difficulties and level of anastomosis deserve a close clinical observation with appropriately timed surgical reintervention.

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REFERENCES

1   **Efron EF**, Vernava III AM. Reoperative surgery for acute colorectal anastomotic dehiscence and persistent abdominal sepsis. In: Longo WE, Northover JMA. Reoperative colon and rectal surgery. London: Martin Dunitz Ltd, 2003: 1-26

2   **Golub R**, Golub RW, Cantu R, Stein HD. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. *J Am Coll Surg* 1997; **184**: 364-372

3   **McArdle CS**, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. *Br J Surg* 2005; **92**: 1150-1154

4   **Rullier E**, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg* 1998; **85**: 355-358

5   **Sørensen LT**, Jørgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jørgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. *Br J Surg* 1999; **86**: 927-931

6   **Vignali A**, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, Strong SA, Oakley JR. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. *J Am Coll Surg* 1997; **185**: 105-113

7   **Nesbakken A**, Nygaard K, Lunde OC. Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. *Br J Surg* 2001; **88**: 400-404

8   **Alves A**, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. *World J Surg* 2002; **26**: 499-502

9   **Benoist S**, Panis Y, Alves A, Valleur P. Impact of obesity on surgical outcomes after colorectal resection. *Am J Surg* 2000; **179**: 275-281

10 **Fawcett A**, Shembekar M, Church JS, Vashisht R, Springall RG, Nott DM. Smoking, hypertension, and colonic anastomotic healing; a combined clinical and histopathological study. *Gut* 1996; **38**: 714-718

11 **Platell C**, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. *Colorectal Dis* 2007; **9**: 71-79

12 **Debas HT**, Thomson FB. A critical review of colectomy with anastomosis. *Surg Gynecol Obstet* 1972; **135**: 747-752

13 **Sutton CD**, Marshall LJ, Williams N, Berry DP, Thomas WM, Kelly MJ. Colo-rectal anastomotic leakage often masquerades as a cardiac complication. *Colorectal Dis* 2004; **6**: 21-22

14 **Alves A**, Panis Y, Pocard M, Regimbeau JM, Valleur P. Management of anastomotic leakage after nondiverted large bowel resection. *J Am Coll Surg* 1999; **189**: 554-559

15 **Eckmann C**, Kujath P, Schiedeck TH, Shekarriz H, Bruch HP. Anastomotic leakage following low anterior resection: results of a standardized diagnostic and therapeutic approach. *Int J Colorectal Dis* 2004; **19**: 128-133

16 **Nicksa GA**, Dring RV, Johnson KH, Sardella WV, Vignati PV, Cohen JL. Anastomotic leaks: what is the best diagnostic imaging study? *Dis Colon Rectum* 2007; **50**: 197-203

17 **DuBrow RA**, David CL, Curley SA. Anastomotic leaks after low anterior resection for rectal carcinoma: evaluation with CT and barium enema. *AJR Am J Roentgenol* 1995; **165**: 567-571

18 **Akyol AM**, McGregor JR, Galloway DJ, George WD. Early postoperative contrast radiology in the assessment of colorectal anastomotic integrity. *Int J Colorectal Dis* 1992; **7**: 141-143

19 **Hyman N**, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg* 2007; **245**: 254-258

20 **Junger W**, Junger WG, Miller K, Bahrami S, Redl H, Schlag G, Moritz E. Early detection of anastomotic leaks after colorectal surgery by measuring endotoxin in the drainage fluid. *Hepatogastroenterology* 1996; **43**: 1523-1529

21 **Miller K**, Arrer E, Leitner C. Early detection of anastomotic leaks after low anterior resection of the rectum. *Dis Colon Rectum* 1996; **39**: 1081-1085