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REVIEW

Prediction and diagnosis of colorectal anastomotic leakage: A systematic review of literature

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Abstract

Although many studies have focused on the preoperative risk factors of anastomotic leakage after colorectal surgery (CAL), postoperative delay in diagnosis is common and harmful. This review provides a systematic overview of all available literature on diagnostic tools used for CAL. A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. Articles were selected when a diagnostic or prediction tool for CAL was described and tested. Two reviewers separately assessed the eligibility and level of evidence of the papers. Sixty-nine articles were selected (clinical methods: 11, laboratory tests: 12, drain fluid analysis: 12, intraoperative techniques: 22, radiology: 16). Clinical scoring leads to early awareness of probability of CAL and reduces delay of diagnosis. C-reactive protein measurement at postoperative day 3-4 is helpful. CAL patients are characterized by elevated cytokine levels in drain fluid in the very early postoperative phase in CAL patients. Intraoperative testing using the air leak test allows intraoperative repair of the anastomosis. Routine contrast enema is not recommended. If CAL is clinically suspected, rectal contrast-computer tomography is recommended by a few studies. In many studies a "no-test" control group was lacking, furthermore no golden standard for CAL is available. These two factors contributed to a relatively low level of evidence in the majority of the papers. This paper provides a systematic overview of literature on the available tools for diagnosing CAL. The study shows that colorectal surgery patients could benefit from some diagnostic interventions that can easily be performed in daily postoperative care.

Key words: Colorectal; Anastomosis; Leakage; Diagnosis; Prediction

Core tip: Postoperative delay in diagnosis of colorectal anastomotic leakage is common and harmful. This paper provides a systematic overview of literature on the available tools for diagnosing colorectal surgery. The study shows that colorectal surgery patients could benefit from some diagnostic interventions that can easily be performed in daily postoperative care.

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INTRODUCTION

Anastomotic leakage is the most frequent major adverse event after colorectal surgery and remains a large burden for patients and surgeons[1]. Despite evolutions in stapling techniques and operation modalities, incidence of anastomotic leakage after colorectal surgery (CAL) has not decreased over the last decade[1,2]. In the abundant literature on CAL, figures on incidence vary widely, most probably because many studies did not apply the unequivocal definition of CAL that has been available since 2010[3,4]. Clinical signs of CAL before the fifth postoperative day (POD) are uncommon, and most studies described a mean POD of 8 d for CAL to become clinically apparent. However, some studies even show that CAL is diagnosed at mean POD 12[5,6]. Short-term morbidity and mortality, as well as detrimental long-term effects, such as permanent stoma, might be reduced if CAL is detected and treated in an early phase[7]. Many studies have focused on preoperative risk factors, such as age, sex, neoadjuvant therapy, emergency surgery and distance to the anal verge, and should enable an estimation of risk of postoperative CAL[8-11]. Despite this caution, delay in diagnosis is common and has been described to be caused by false negative radiological investigation and intervening weekends[12]. This study was designed to provide colorectal surgeons with a systematic review of the predictive value of the diagnostic techniques for detection of CAL that are currently described in literature.

METHODS OF STUDY

Search methods

A systematic search of literature was undertaken using Medline, Embase, Cochrane and Web-of-Science libraries. No limitations for year of publication were applied. Search terms were: anastomosis, leakage, dehiscence, colorectal, rectum, resection, anterior resection, diagnosis, sensitivity, specificity, prediction, forecasting, monitoring. The search was restricted to publications in English and French. Full search syntax is shown in Addendum and was carried out lastly on 15 October, 2012. All references in eligible articles were screened for additional publications. Articles were retrieved according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses guidelines (Figure 1).

Study selection

Articles were selected if a diagnostic tool or prediction model for CAL was described and tested, preferably using a reference. Furthermore, definition of CAL was required. If an article described more than one diagnostic tool, it was included for all the tools that were addressed, with the exception of the technique serving as reference/golden standard.

Studies were excluded if they reported on risk prediction of other complications than CAL. The included anastomosis were ileo-colic, colo-colic, colorectal and colo-anal. Total coloproctectomy with ileal pouch anal anastomosis was excluded since etiology, diagnosis and treatment are very different from the types of anastomosis mentioned before. Moreover, studies on risk factors for CAL and randomized trials studying treatment modalities were excluded, as were presentations, experimental studies, narrative reviews and letters to the editor.

Data extraction

For all eligible studies, a standard data extraction form was filled in and the following data were extracted: study design, number of patients, percentage of clinically important CAL, diagnostic tool and main results. If published, sensitivity, specificity, positive predictive value and negative predictive value were noted, or, if possible, calculated. If stated, the POD of CAL diagnosis was recorded. Furthermore, two authors (Daams, Wu) separately determined the level of evidence for validation studies according to the Levels of Evidence 2011 from the Centre for Evidence Based Medicine. In case of inconsistencies, agreement was accomplished by discussion.

RESULTS OF STUDY

The abstracts of a total of 859 articles were screened separately by 2 authors (Daams, Wu) for eligibility. Of these article, 771 were excluded, either for being written in a different language than French and English (n = 25), or for description of preoperative risk factors for CAL (n = 90), or due to irrelevance (n = 308), or because they described a patient cohort or randomized trial or experimental studies, or for other reasons than early detection of CAL (n = 348). This resulted in 88 articles, 18 of which were excluded after full text examination, either for being a narrative review (n = 3), or abstract (n = 11), or due to irrelevance (n = 4).

The remaining 70 articles were included and subdivided into 5 groups, according to type of method used. Two studies were included in two different groups, some studies related to more than one diagnostic tool from one category. (1) Clinical methods: Eleven articles focused on clinical methods, such as the value of physical examination (n = 1), the correlation between clinical symptoms and CAL (n = 5), the application of CAL risk scores (n = 2) or the direct postoperative prediction of the risk of CAL by the surgeon (n = 3); (2) laboratory tests: Twelve articles related to the correlation between CAL and postoperative levels of cytokines (n = 1), C-reactive protein (CRP, n = 10) or coagulation parameters (n = 1); (3) drain fluid analysis: Twelve articles related to diagnosis of CAL by analysing peritoneal drain fluid, in one case using two different methods in one study. The articles focussed on macroscopic findings of drain production (n = 2) or on drain fluid analysis of cytokine levels (n = 6), lipopolysaccharides levels (n = 1) or lysozym levels (n = 1). One article addressed the topic of intramucosal pH-measurement, and two articles focused on microdialysis of the peritoneal cavity; (4) intra-operative techniques: Twenty-three articles investigated the correlation between preop-

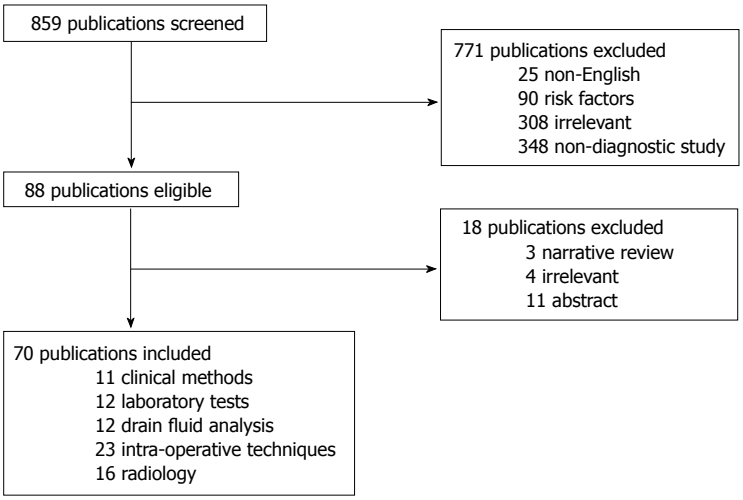

Figure 1 Preferred items for reporting of systematic reviews and meta-analyses-chart for included articles. Two articles could be included in two subgroups.

erative assessment of the anastomosis and CAL, using one or more of the following techniques: air/methylene blue leak test (ALT, n = 13), intraoperative endoscopy (IOE, n = 4), Doppler ultrasound (n = 2), tissue oxygen tension measurement (n = 1), intraoperative inspection of marginal artery bleeding (n = 1), laser fluorescence angiography (LFA, n = 1) and near infra-red/visible light spectroscopy (n = 2); and (5) radiology: Sixteen studies evaluated the accuracy of one or more of the following radiological techniques in detecting CAL: computer tomography (CT, n = 7), water-soluble contrast enema (WSCE, n = 10) and plain X-ray (n = 2).

Clinical methods

Table 1 gives an overview of the main results of the eleven included studies. Three studies described direct postoperative CAL risk prediction by the surgeon. Two studies described direct postoperative assessment by the surgeon as valuable[13,14]. Karliczek *et al*[15] prospectively studied subjective assessment of the risk of CAL by the surgeon directly after surgery. Low predictive values were found, with a sensitivity of 62% and a specificity of 52% for low rectal anastomosis.

Five studies analysed the postoperative clinical course of patients with CAL in comparison to patients with an uncomplicated course. Two retrospective studies noted that occurrence of respiratory and neurological disorders often precede CAL after colonic surgery (OR = 2.8 and 5.3 respectively)[16,17]. One prospective study noted that cardiac disorders preceded CAL in 40% of 22 patients with CAL[18]. A small study reported no differences in heart rate variability between patients with and without CAL[19]. In a prospective study by Nesbakken *et al*[20], the postoperative assessment of the patient by the surgeon was reported to have high specificity and low sensitivity (91% and 50% respectively). Tang *et al*[21] investigated the value of digital rectal examination in assessing CAL before stoma closure, and found a sensitivity of 98.4%.

Two Dutch authors developed and applied leakage scores for the detection of CAL. One risk score prospectively combined preoperative and intraoperative items and yielded a twofold higher score in patients with CAL than in patients without CAL[22]. For postoperative clinical course assessment, a standardized leakage score was developed by den Dulk *et al*[23] attributing points to certain clinical factors, nutritional status and biochemic findings, thus identifying high risk patients. It facilitated the diagnosis of CAL at POD 6, as opposed to POD 8 in a historical control group.

Laboratory tests

Ten studies investigated the correlation between postoperative levels of CRP and CAL as shown in Table 2[24-28]. Five of them were included in a meta-analysis of 1832 patients by Warschkow *et al*[24], which did not focus solely on CAL but on all postoperative infectious complications. In all studies, CRP-levels were elevated several days before the diagnosis of CAL was established. Slotwinski and colleagues reported higher levels of soluble-tumour necrosis factor (TNF)-receptor at POD 1 in patients who developed CAL after colorectal surgery[29]. Iversen *et al*[30] studied levels of markers of coagulation and fibrinolysis in patients with CAL showed elevated levels 5-6 PODs before clinical onset of CAL compared to patients without leakage.

Drain fluid analysis

Table 3 shows twelve studies on drain fluid analysis. Six out of twelve studies investigated cytokine levels after colorectal surgery, mainly focussing on interleukin (IL)-6, IL-10 and TNF-α. In 4 of these studies, patients after colorectal surgery who developed CAL at POD 5-20 had elevated cytokine levels from POD 1 onwards[31-34]. One study reported the same phenomenon, but the onset of increased cytokine levels was POD 3[35]. Another study did not find a relation between CAL and levels of IL-6 and TNF-α[36]. In two studies describing the technique of microdialysis, local signs of ischemia were measured before CAL became clinically apparent in some patients, although both studies also describe patients with CAL who showed no preceding abnormal microdialysis values[33,37]. Macroscopic changes in drain production were

Table 1 Clinical methods

Author	Type of study	Loe	*n* (CAL/non-CAL)	Colorectal/rectum	Stapled/handsewn anastomosis	Study subject/tool		Se	Sp	PPV	NPV	ROC	Main outcome
Dekker *et al*[22]	Pro	3b	10/121	Colorectal	?	Leakage score		-	-	-	-	0.95	OR = 1.74 for leakage score predictive of CAL
den Dulk *et al*[23]	Pro	2b	21/223	Colorectal	Both	Leakage score		-	-	-	-	-	Delay of treatment reduced from 4 d to 1.5 d
Sutton *et al*[18]	Pro	3b	22/398	Colorectal	?	Clinical symptoms		0.33	0.97	0.59	0.93		Over 40% of patients with cardiac event has CAL
Haase *et al*[19]	Pro	4	3/40	Colorectal	?	Clinical symptoms		-	-	-	-	-	No difference in heart rate variability between CAL and non-CAL
Ghariani *et al*[17]	Retro	3b	23/314	Colon	?	Clinical symptoms		-	-	-	-	-	Respiratory, neurological disorders and bloating precipitate CAL
Bellows *et al*[16]	Retro	3b	25/311	Colorectal	?	Clinical symptoms	Respiratory symptoms	0.52	0.84	0.22	0.95	-	Respiratory, neurological disorders and abdominal pain and distension precipitate CAL
							Neurology symptoms	0.24	0.97	0.4	0.94	-	
							Abdominal pain and distension	0.52	0.83	0.21	0.95	-	
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	Clinical symptoms	Daily assessment by surgeon	0.50	0.89	0.5	0.89	-	50% of CAL is silent
Tang *et al*[21]	Pro	3b	10/195	Rectum	Both	Digital rectal examination		0.98	-	-	-	-	As valuable as WSCE before stoma closure
Pettigrew *et al*[13]	Pro	3b	28/113	Colorectal and general	?	Risk prediction by surgeon		0.38	0.91	0.56	0.82		Highest predictive value for postop surg assessment
Makela *et al*[14]	Retro	3b	44/88	Rectum	Both	Risk prediction by surgeon		-	-	-	-	-	In 86% of pts with > 3 risk factors CAL occurs
Karliczek *et al*[15]	Pro	3b	26/191	Colorectal	?	Risk prediction by surgeon	High anastomosis	0.38	0.46	-	-	-	Low predictive value for prediction of CAL by surgeon
							Low anastomosis	0.62	0.52	-	-	-	

Pro: Prospective; Retro: Retrospective; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; ROC: Receiver-operating characteristic curve; WSCE: Water soluble contrast enema.

examined by Tsujinaka *et al*[38]. Of 21 patients with CAL, 15 had previous changes in drain content, while other clinical signs were not obvious. Likewise, Eckmann *et al*[39] found that 80% patients that developed CAL after rectum resection had changes in drain fluid aspect. By measuring intramucosal pH, Millan *et al*[40] found that the risk of CAL was 22 times higher when juxta-anastomotic intramucosal pH was below 7.28. In a small study, intraperitoneal levels of lipopolysaccharides were elevated from POD 3 in patients with CAL, while CAL was only clinically evident at mean POD 6, 7[41]. By contrast, lysozyme activity was not correlated with clinical CAL in another small study[42].

Intra-operative techniques

Table 4 demonstrates the studies on intraoperative techniques to detect CAL. Thirteen studies on peroperative leak tests were evaluated[43-55]. Although these tests facilitate intraoperative repair of the anastomosis or creation of faecal diversion in case of air leakage or methylene blue leakage, postoperative leakage rates were not reduced to 0%. A study by Beard, reported on 18 intraoperative anastomotic corrections, leading to CAL in 3 patients in the "test"-group, compared to 10 patients with CAL in the "no test"-group[43]. As with the air leak test, colonoscopy, performed in 4 studies, led to intraoperative correction of the anastomosis for reasons of leakage and bleeding[52,56-58]. All studies reported low incidences of CAL, although no study compared intraoperative colonoscopy to no intraoperative control. Two studies comparing routine intraoperative colonoscopy to selective use of this technique showed no benefit of routine application of this technique[57,58]. For assessing local anastomotic blood flow, multiple techniques have been described. Ambrosetti *et al*[59] studied the use of Doppler intraoperatively at the site of the anastomosis, enabling correction of the anastomosis in 10 of 200 patients, leading to CAL in 2 (1%). Vignali *et al*[60] found

Table 2 Laboratory tests

Author	Type of study	Loe	*n* (CAL/non-CAL)	Colorectal/rectum	Stapled/handsewn anastomosis	Study subject/tool	Cut-off value	Se	Sp	PPV	NPV	ROC	Main outcome	Onset CAL (POD)
Slotwinksi *et al*[29]	Pro	3b	2/16	Colorectal	?	sTNF-R1, IL-1RA/-6/-8/-10, CRP	-	-	-	-	-	-	TNF higher at POD 1 in CAL	?
Iversen *et al*[30]	Pro	3b	17/34[1]	Colorectal	Both	s-Fibrin, TAT-complex, PT-f1/-2	-	-	-	-	-	-	PT-f1/-2, TAT-complex, s-Fibrin higher at POD 1/2 in CAL	7
Woeste *et al*[25]	Retro	3b	26/342	Colorectal	Both	CRP	-	-	-	-	-	-	CRP higher from POD 3 to POD 7 in CAL	8,7
Warschkow *et al*[24]	Meta	3a	?/1832	Colorectal	Both	CRP	135 mg/L at POD 4	0.680	0.830	0.560	0.89	-	CRP < 135 mg/L at POD 4 discharge is safe	?
Kornerin *et al*[24]	Retro	3b[3]	18/231	Colorectal	Both	CRP	190 mg/L at POD 3	0.820	0.730	-	-	0.820	Persisting elevation of CRP is indicative for CAL	8
Mackay[in] *et al*[24]	Pro	3b[3]	5/160	Colorectal	?	CRP	145 mg/L at POD 4	0.850	0.860	0.610	0.96	-	CRP > 145 mg/L at POD 4 is highly predictive for CAL	?
Ortega[in] *et al*[24]	Pro	3b[3]	21/133	Colorectal	Both	CRP	125 mg/L at POD 4	0.820	0.960	-	-	-	CRP > 125 mg/L at POD 4 discharge is not safe	6
Welsch[in] *et al*[24]	Pro	3b[3]	22/96[1]	Rectum	Staples	CRP	140 mg/L at POD 3	0.80[2]	0.81[2]	0.86[2]	-	-	Persisting elevation of CRP is indicative for CAL	8
Warschkow[in] *et al*[24]	Retro	3b[3]	89/1115	Colorectal	?	CRP	143 mg/L at POD 4	0.750	0.710	0.190	0.97	-	Use CRP as screening at POD 4	9
Platt *et al*[26]	Pro	3b	26/454	Colorectal	Both	CRP	190 mg/L at POD 3	0.772	0.80[2]	-	-	0.89[2]	CRP at POD 3 is useful for predicting CAL	6-8
Matthiessen *et al*[27]	Pro	3b	9/33	Rectum	?	CRP	-	-	-	-	-	-	CRP higher from POD 2 in CAL	8
Almeida *et al*[28]	Retro	3b	24/149	Colorectal	?	CRP	140 mg/L at POD 3	0.780	0.860	-	-	-	CRP sign higher from POD 2 in CAL	7

[1]Selected groups; [2]All complications; [3]Included in meta-analysis. Pro: Prospective; Retro: Retrospective; Meta: Meta-analysis; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; TNF: Tumour necrosis factor; IL: Interleukin; CRP: C-reactive protein; TAT: Thrombin-antithrombin complexes; PT: Prothrombin; POD: Postoperative day; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; ROC: Receiver-operating characteristic curve.

that reduced microperfusion at the rectal stump, during creation of a colorectal anastomosis, measured by laser Doppler increased the risk of CAL. In a study by Kudszus *et al*[61] intraoperative LFA led to 28 intraoperative corrections, an absolute reintervention rate of 4% and reduced hospital stay. Hirano *et al*[62] studied the application of near infrared spectroscopy of the anastomosis. In their small study, perianastomotic StO_2 < 60 mmHg was measured in patients who developed CAL. In a similar study by Karliczek *et al*[63], using visible light spectroscopy, changes in perianastomotic pO_2 before and after creation of the anastomosis had a significant correlation with CAL. One study showed that reduced pO_2 in perianastomotic tissue was predictive for CAL, although cut-off values for routine clinical application were lacking[64,65].

Radiology

Table 5 demonstrates sixteen studies evaluated several imaging modalities for the detection of CAL. Seven studies in this review used computed tomography (CT) for the detection of CAL[20,66-78]. A prospective study by Nesbakken *et al*[20] reported a 94% accuracy for 5 patients with CAL out of 56 patients who had received rectum resection. Similarly, Eckman *et al*[77] concluded that CT detected 29 of 30 leaks in a group of 305 patients after stapled rectum resection, although no data were presented on the specificity of the technique. Gouya *et al*[75]

Table 3 Drain fluid analysis

Aauthor	Type of study	Loe	*n* (CAL /non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study subject/tool	Main outcome	Onset CAL (POD)
Bertram *et al*[36]	Pro	4	3/28	Colorectal	?	Cytokines	No correlation between IL-6, TNF-alpha and CAL	5.3
Herwig *et al*[34]	Pro	3b	12/24	Colorectal	?	Cytokines	IL-6 and TNF-alpha elevated from POD 1 in CAL	5.8
Yamamoto *et al*[35]	Pro	3b	7/90	Colorectal	Stapled	Cytokines	IL-1beta, IL-6, TNF-alpha elevated from POD 3 in CAL	5-8
Ugras *et al*[32]	Pro	3b	4/34	Colorectal	Both	Cytokines	IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	6
Fouda *et al*[31]	Pro	3b	8/56	Rectum	Both	Cytokines	IL-6, IL-10 elevated from POD 1 in CAL, TNF-alpha elevated from POD 2 in CAL	6
Mattiessen *et al*[33]	Pro	3b	7/23	Rectum	?	Microdialysis, cytokines	L/P-ratio elevated at POD 5/6 in CAL; IL-6, IL-10, TNF-alpha elevated from POD 1 in CAL	Early CAL: 6 Late CAL: 20
Ellebaek *et al*[37]	Pro	3b	4/50	Colorectal	?	Microdialysis	Mean L/P-ratio higher in CAL,	Early CAL: 5-10 Late CAL: 20
Tsujinaka *et al*[38]	Pro	3b	21/196	Rectum	Both	Drainproduction	15/21 Patients with CAL had changes in drain content	7
Eckmann *et al*[39]	Retro	3b	30/306	Rectum	Stapled	Drainproduction	80% of leakages were indicated by drain, 40% of which prior to clinical symptoms	?
Millan *et al*[40]	Pro	3b	6/90	Colorectal	Stapled	Intramucosal pH	Intramucosal pH < 7.28 on POD1 increases risk of CAL 22 fold	?
Junger *et al*[41]	Pro	3b	3/22	Colorectal	Both, biodegradable ring	LPS	Excretion of LPS and LPS concentration is higher at POD 3 in CAL	6,7
Miller *et al*[42]	Pro	2b	2/42	Rectum	Stapled	Lysozym activity	No correlation between lysozyme activity and CAL	?

Pro: Prospective; Retro: Retrospective; Loe: Level of evidence; CAL: Colorectal anastomotic leakage; LPS: Lipopolysaccharides; IL: Interleukin; TNF: Tumour necrosis factor; POD: Postoperative day.

even reported an excellent 100% sensitivity and specificity. However CT will only show leakage of intraluminal contrast at the site of the CAL in 10% of the patients[67]. Improved results are achieved with the detection of associated features such like pericolic/pelvic fluid collections[78]. Presacral abnormalities, commonly described as caused by leakage, were found in 70% of the patients without clinical anastomotic leakage[68].

Ten studies investigated the value of the water-soluble contrast enema in determining CAL, mostly after rectum resection, both in the postoperative phase and before closure of deviating ileostomy[20,66,67,69-75]. All studies described a high degree, in one case even up to 41%[72], of asymptomatic radiological leakage that resolved without therapeutic intervention. In addition, no study performed contrast enemas in the very early postoperative phase (< POD 5) due to the potential risk of complications so that, when performed at POD 7, 8, a clinical leakage concurred with radiological leakage. For these reasons, most studies concluded that routine application of WSCE at POD 7, 8 did not contribute to clinical decision-making or to early detection. In the presence of clinical signs suggestive for CAL, a study by Nesbakken *et al*[20] described an accuracy of 93% for WSCE in the detection of CAL. Doeksen *et al*[67] reported a high specificity and positive predictive value of 94% and 91% respectively, with an interobserver variability of 14%.

Two studies investigated the value of plain X-ray. One of these studies reported that increase of subdiafragmatical free air after POD5 increased the likelihood of CAL[76]. The other study, by Williams *et al*[79], reported that the finding of staple line disruption on plain X-ray was suggestive for CAL.

In this paper, all available evidence on the diagnostic tools for detection of CAL was systematically reviewed, according to the guidelines of the Oxford Centre of evidence based medicine. Diagnostic techniques were appraised for their ability to predict or detect clinically relevant CAL, since this is relevant in daily care for patients directly after colorectal surgery. Early intervention in abdominal sepsis is essential as is shown by the Surviving Sepsis Campaign, emphasizing on source identification and surgical control when possible[80].

Many studies report data on asymptomatic or radiological CAL. However, these data were not included in this review, since asymptomatic CAL, if detected, will be left untreated as a rule. Furthermore, it has a poor correlation with clinically relevant CAL. Theoretically, asymptomatic CAL might prove to be important if the oncologic outcome is studied, since equivocal literature is available showing a higher percentage of local recurrence after CAL[81-83]. To this date, however, the role of asymp-

Table 4 Intra-operative techniques

Author	Type of study	Loe	*n* (CAL/non-CAL	Colorectal/rectum	Stapled/handsewn anastomosis	Test	Test performed	Test +	Intra-operative correction	CAL test +	Test -	CAL test -	Test not performed	CAL test not performed	Main outcome
Beard *et al*[43]	Pro	1b	13/145	Colorectal	Both	ALT	73	18	18	3	55	0	70	10	ALT and preoperative repair reduce risk of AL
Davies *et al*[44]	Pro	3b	4/33	Rectum	?	ALT	33	6	6	1	27	3	-	-	LT helpful to reduce leakage rate
Dixon *et al*[45]	Retro	3b	2/202	Rectum	Both	ALT	119	5	5	0	114	0	-	-	Leaks were avoided
Gilbert *et al*[46]	Retro	3b	1/21	Colorectal	Handsewn	ALT	21	5	5	1	16	0	-	-	ALT facilitates IOR
Lazorthes *et al*[47]	Pro	3b	3/82	Colorectal	Stapled, doughnut complete 68	ALT	68	0	0	0	68	3	-	-	High NPV for ALT
					Stapled, doughnut incomplete 14		14	4	4	0	10	0	-	-	
Ricciardi *et al*[48]	Retro	3b	48/998	Colorectal	Both	ALT	825	65	65	5	760	29	173	14	ALT for leftsided anastomosis
Schmidt *et al*[49]	Pro	3b	68/933	Rectum	Both	ALT	260	47	42	5	213	22	36	4	Risk of AL is unrelated to ALT
Wheeler *et al*[50]	Pro	4	7/102	Colorectal	?	ALT	99	21	21	2	85	2	-	-	LT facilitates IOR
Yalin *et al*[51]	Po	3b	1/23	Colo-rectal	Stapled	ALT	21	5	5	1	16	0	-	-	LT facilitates IOR
Griffith *et al*[54]	Pro	4	2/60	Colorectal	Stapled	ALT	60	11	11	0	49	2	-	-	ALT facilitates IOR
Sakanoue *et al*[55]	Pro	3b	4/70	Rectum	?	ALT	35	2	2	0	33	0	35	4	Useful for intraoperative decision making
Smith *et al*[53]	Pro	4	7/229	Colon	Both	ALT	229	16	16	0	213	7	-	-	After IOR no CAL occurred
Lanthaler *et al*[56]	Pro	3b	6/122	Colorectal	Stapled	IOE	73	5	5	0	68	4	49	2	ALT prevents early leak
Li *et al*[57]	Pro	3b	2/244	Rectum	Stapled	IOE	107	11	11	0	96	0	137, 30 IOC[1]	2/137, 1/30	Routine IOE and selective IOE equal results
Shamiyeh *et al*[58]	Pro	3b	7/253	Rectum	Stapled	IOE	85	2	2	0	83	1	253	4	Routine IOE does not reduce CAL
Ishihara *et al*[52]	Pro	4	1/73	Rectum	Stapled	IOE and ALT	73	4	4	0	69	1	-	-	ALT recommended
Ambrosetti *et al*[59]	Pro	4	2/200	Colorectal	Both	Doppler ultra-sound									Doppler facilitates IOR
Vignali *et al*[60]	Pro	3b	8/55	Colorectal	Stapled	Laser doppler	-	-	-	-	-	-	-	-	Reduction in microperfusion increases risk of CAL
Kudszus *et al*[61]	Retro	3b	22/402	Colorectal	Both	LFA	201	28	28	8	-	-	201	15	LFA reduces reoperation rate for AL, most prominent in handsewn
Hirano *et al*[62]	Pro	4	1/20	Colorectal	?	Near infrared spectro-scopy									StO_2 < 60% in CAL

Novell *et al*[64]	Pro	3b	275	Colorectal	Both	Obser-vation of marginal artery bleeding					Pulsatile flow: lower incidence CAL
Sheridan *et al*[65]	Pro	3b	5/50	Colon	?	Tissue pO_2 measurement					Reduced anastomotic pO_2 predictive CAL
Karliczek *et al*[63]	Pro	3b	14/77	Colorectal	?	Visible light spectro-scopy					pO_2 could predict CAL

[1]Indicated by the surgeon. Pro: Prospective; Retro: Retrospective; Exp: Experimental (model); Loe: Level of evidence; CAL: Colorectal anastomotic leakage; ALT: Air or methylene blue leak test; IOC: Intra-operative endoscopy; LFA: Laser fluorescence angiography; IOR: Intra-operative repair; NPV: Negative predictive value.

Table 5 Radiology

Author	Type of study	Loe	*n* (CAL/ non-CAL)	Colorectal/ rectum	Stapled/ handsewn anastomosis	Study tool	Se	Sp	PPV	NPV	Main outcome
Eckmann *et al*[77]	Retro	3b	30/306	Rectum	Stapled	CT	-	-	-	-	29 of 30 CAL detected by CT
Power *et al*[78]	Retro	3b	17/50	Colorectal	?	CT	0.30	0.90	0.58	0.74	Peri-anastomotic located fluid containing air found in CAL
Gouya *et al*[75]	Retro	3b	10/195	Rectum	?	CT	-	-	1.00	1.00	CT has role in predicting CAL
DuBrow *et al*[68]	Retro	3b	35/75	Rectum	?	CT	-	-	-	-	30% of pts with CAL have presacral abnormalities
Nicksa *et al*[73]	Retro	4	36 CAL	Rectum	?	CT	0.12	-	-	-	Low percentage true positives
Doeksen *et al*[67]	Retro	3b	68/429	Colorectal	?	CT	0.54	0.78	0.68	0.66	Interobserver variability 10%
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	CT	0.57	1.00	-	-	94% accuracy of CT for detection of CAL
Severini *et al*[74]	Retro	3b	12/175	Rectum	?	WSCE	-	-	-	-	2 CAL out of 78 positive WSCE, low predictive value
Hoffmann *et al*[70]	Retro	3b	5/51	Colorectal	Both	WSCE	0.20	0.85	0.13	0.91	WSCE not recommended for routine use
Markham *et al*[72]	Retro	3b	1/136	Rectum	Handsewn	WSCE	1.00	0.57	0.02	1.00	WSCE no contribution to surgical management
Kalady *et al*[71]	Retro	3b	8/211	Rectum	?	WSCE	0.88	1.00	1.00	0.99	WSCE does not provide additional information
Akyol *et al*[66]	Pro	3b	12/233	Colorectal	Both	WSCE	0.52	0.87	0.30	0.94	WSCE provides little useful clinical information
Haynes *et al*[69]	Retro	3b	14/117	Colorectal	Both	WSCE	0.71	0.86	0.42	0.96	WSCE not recommended for routine use
Gouya *et al*[75]	Retro	3b	10/195	Rectum	?	WSCE	-	-	1.00	0,98	WSCE is recommended for routine use
Nicksa *et al*[73]	Retro	4	36 CAL	Rectum	?	WSCE	0.88	-	-	-	WSCE superior to CT
Doeksen *et al*[67]	Retro	3b	68/429	Colorectal	?	WSCE	0.68	0.94	0.91	0.76	Interobserver variability 13%
Nesbakken *et al*[20]	Pro	3b	5/56	Rectum	?	WSCE	0.60	1.00	-	-	93% accuracy of WSCE for detection of CAL
Williams *et al*[76]	Retro	4	10/31	Rectum	Stapled	X-ray	0.90	1.00	1.00	0.95	Staple line dehiscence in 9/10 patients with CAL
Tang *et al*[79]	Pro	4	2/64	Colorectal	?	X-ray	-	-	-	-	Increase free air after POD 5 higher chance CAL

Pro: Prospective; Retro: Retrospective; Meta: Meta-analysis; Leo: Level of evidence; CAL: Colorectal anastomotic leakage; CT: Computer tomography; WSCE: Water-soluble contrast enema; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; POD: Postoperative day.

tomatic CAL in local recurrence is unknown.

Two investigators separately evaluated all eligible studies and a level of evidence was assigned to each of them. Overall, the level of evidence was considered low. This was due to factors that coincide with the problem of CAL. First, in the field of the diagnosis of CAL, no definition of CAL is available, nor is a golden standard[3]. Such a golden standard cannot even be found in relaparotomy during which faecal discharge at the site of the anastomosis is established, since many patients are treated for CAL without direct visualization of the anastomosis during reoperation. Secondly, a major cause of the low level of evidence is the fact that many studies lack a non-test group. Finally, guidelines to determine the level of evidence differ between diagnostic studies and their therapeutic counterparts. Publication bias and reporting bias in particular were estimated to be low, since the primary search yielded many studies with negative results and small numbers of subjects.

Much research has been done on the early detection of leakage after ileoanal pouch reconstruction following total colectomy for inflammatory bowel disease. These studies were excluded from this review, since they comprise more extensive surgery, different types of leakage, other types of pouch failure and different therapy modalities.

Clinical methods

Clinical factors are objective and easily available for risk prediction. A few problems, however, occur if surgeons rely solely on clinical factors. First, the influence of individual factors is not exactly known. Secondly, by the time signs of septicaemia occur; patients will be in a worse clinical state at the onset of an often prolonged and onerous therapeutic course. Subjective prognosis of leakage at the moment of finishing the anastomosis was proven to have a limited prognostic value[15]. Objective measurements might be of greater prognostic value, as shown by the Colon Leakage Score, in which the presence of objective risk factors leads to a higher score representing a higher chance of CAL[22]. This leakage score was based on previously identified risk factors and to our knowledge is the first to translate all available literature on risk factors for CAL into an instrument that can easily be implemented in daily practice. In a cohort of 233 patients, using a historical control group of 1066 patients, den Dulk *et al*[23] developed a similar score system for postoperative clinical evaluation of the colorectal patient. When a high score is found, computer tomography using rectal contrast is warranted. Although this promising method has shown to reduce delay in diagnosis, no information was provided on the prognostic value of this risk score, nor did the study mention the number of CT-scans and concomitant negative results In a study on tracking of surgical site infections (SSI), van Ramshorst *et al*[84] found that protocolled tracking yields a higher reported incidence of SSI than self-reported detection. We believe that this finding could be applied to the protocolled detection of CAL as described above, as it contributes to increased awareness and early detection. Little is known about the value of physical examination in relation to CAL, except that digital rectal examination has at least the same prognostic value for low anastomosis as contrast enema prior to stoma reversal.

Laboratory tests

Many investigators have studied the behaviour of CRP during the subclinical phase of CAL. CRP has the capacity to rise quickly after the onset of an inflammatory stimulus, reaching its highest serum level within 48 h. Since it has a short halftime of around 19 h, a drop in CRP corresponds well with the removal of the stimulus. Most studies investigating CRP used cut-off values of around 120-190 mg/L at POD 3, 4, and all studies in this review showed a reasonable predictive value of CRP for CAL. Drawbacks of all studies described in this review is that the number of included patients per study is rather small and that none of these studies provide a protocol that structurally describes the postoperative clinical examination, the clinical state of the patients during postoperative follow-up and the type of CAL (*i.e.*, faecal peritonitis, juxta-anastomotic abscess, rectovaginal fistula). Despite these drawbacks, we believe that these studies have indeed shown that measurement of CRP is of great importance in detecting CAL in the preclinical phase.

Other laboratory tests like coagulation factors and cytokines show a correlation with occurrence of CAL, but they have been studied sparsely. Since no parameters for their predictive value can be calculated from the available data, there is no basis for incorporating them in the standard postoperative lab tests.

Drain fluid analysis

In this review, the results for cytokine levels in peritoneal drain fluid, as biomarkers for local infection, seem promising. In most studies cytokine levels were elevated from POD 1 in patients with CAL compared to patients without CAL. This finding suggests an early onset of local infection in patients with CAL, or at least a more prominent postoperative reaction in this group. It is hypothesised that cytokines are directly elevated postoperatively and will normalise unless infectious complications occur. Most frequently investigated cytokines are IL-1, IL-6, IL-10 and TNF-α.

Although routine drainage after colorectal surgery does not seem to prevent CAL and is omitted in enhanced recovery programs, two studies showed that changes of drain production occur frequently and before clinical symptoms. These interesting findings might justify the routine placement of a drain for the first postoperative days as an indicator for CAL.

Two studies on intraperitoneal microdialysis show, by retrospectively analysing of peritoneal microdialysis samples, that CAL was preceded by changes in local lactate/pyruvate ratio. Although these findings are promising, patient numbers were too low to compute predictive values and cut-off values. Future research should elucidate if prospective, real-time analysis actually leads to early detection and determine whether this technique is cost effective.

For intramucosal pH monitoring, as a measure for mucosal hypoperfusion and subsequent hypoxia, data are limited but promising. The same holds for measurement of lipopolysaccharides, integral components of normal gut flora, and measurements of lysozym in drain fluid, since the studies investigating these biomarkers did neither lead neither to confirmation of these techniques nor to a re-evaluation.

Intra-operative techniques

Except for one, all studies evaluating the ALT confirm the importance of this simple intervention. Although not completely eliminating the occurrence of CAL, ALT allows intraoperative revision of the anastomosis, is easy to perform and has a high negative predictive value. Understandably, no studies have been performed that relate a positive ALT without intraoperative repair to CAL. All valuable studies, those that use a no-test control group, show a lower percentage of CAL in the group in which ALT was performed; in two out of four papers this difference was significant.

IOE can, apart from direct visualisation of CAL, be of diagnostic and therapeutical importance if the location of the tumour or of additional lesions is unknown

or if anastomotic bleeding occurs. More recently, the routine application of IOE has been studied in comparison to selective IOE. No favourable results in occurrence of CAL were described for routinely performed IOE compared to selective IOE. Apart from the mentioned benefits of IOE, no data are available on the superiority of IOE compared to ALT for intraoperative diagnosis of anastomotic dehiscence. Thus, ALT seems to be favourable to IOE since it is faster, easier and cheaper.

Some authors have attempted to relate anastomotic perfusion parameters to anastomotic leakage. Except for one, all studies are case controlled without reference and have not been repeated. It has not led to clear cut-off values for any of these techniques that seem not very practical in daily current practice. At least one cohort study with a good reference is needed before clinical implementation.

Radiology

As far as CT with rectal contrast is concerned, only 7 studies could be included. These studies showed large differences in methodology and lacked generally applied definitions. These differences between several studies, especially in CT criteria for CAL, resulted in equivocal results. Intestinal contrast leakage is not regularly depicted with CT in patients with CAL. However CT can accurately depict the associated features of anastomotic leakage such like pericolic/pelvic fluid collections and free air. When these additional criteria were used the accuracy improved dramatically with accuracies varying from 80%-100%.

All six studies that were performed on the subject of WSCE over the last two decades concluded that there is no place for routine application of WSCE. In these studies, WSCE did not have a consistently high positive predictive value, and other techniques, such as digital rectal examination in low rectal anastomosis, appeared to provide at least equal results. Furthermore due to the potential risk of complications no study performed contrast enemas in the very early postoperative phase. This means that, when performed at POD 7-8, clinical CAL concurred with radiological leakage. In addition, radiologic signs of CAL do not correlate with clinical CAL and frequently do not require any form of treatment. Another drawback of WSCE is that the rectally administered contrast has been diluted and there may be not enough remaining pressure to induce contrast leakage in more proximal anastomoses.

Two older studies describe how plain X-rays can be used in assessment of intra-abdominal free air and staple line integrity in the diagnosis of CAL. Although sometimes helpful, modern techniques offer the surgeon much more detailed information on the extend of CAL compared to plain X-rays.

CONCLUSION

Many studies have been performed in the field of diagnosis of CAL. Many lack a no-test control group and reference; therefore the general level of evidence is relatively low. The air leak test is recommended for intraoperative assessment of CAL. When a leakage score system is used intraoperatively, preoperative preventive measures can be taken. When using a clinical algorithm postoperatively, delay in diagnosis of CAL might be reduced. CRP measurement should be part of postoperative laboratory routine at least at POD 3 and 4, since due to a high negative predictive value patients with an uncomplicated course can be identified. Cytokine measurement among other measurements of peritoneal drain fluid is promising and could justify the routine placement of a juxta-anastomotic drain, while peritoneal microdialysis might develop as minimally invasive peritoneal "smart"-drain. When clinical signs are present, CT with rectal contrast is recommended. CT cannot only to detect CAL but also can be used as a therapeutic instrument for percutaneous drainage of a pericolic/pelvic abscess. We believe that this review reaffirms the importance of early detection of colorectal anastomotic leakage and that it offers colorectal surgeons an overview on easily applicable diagnostic tools to improve early detection.

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