Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together

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PII: S1743-9191(16)30970-0

DOI: 10.1016/j.ijsu.2016.09.098

Reference: IJSU 3161

To appear in: *International Journal of Surgery*

Received Date: 24 June 2016

Revised Date: 12 September 2016

Accepted Date: 26 September 2016

Please cite this article as: van Rooijen S, Huisman D, Stuijvenberg M, Stens J, Roumen R, Daams F, Slooter G, Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together, *International Journal of Surgery* (2016), doi: 10.1016/j.ijsu.2016.09.098.

INTRAOPERATIVE MODIFIABLE RISK FACTORS OF COLORECTAL ANASTOMOTIC LEAKAGE

WHY SURGEONS AND ANESTHESIOLOGISTS SHOULD ACT TOGETHER

Running title: intraoperative modifiable risk factors CAL

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Abstract

Background

Colorectal anastomotic leakage (CAL) is a major surgical complication in intestinal surgery. Despite many optimizations in patient care, the incidence of CAL is stable (3-19%).[1] Previous research mainly focused on determining patient and surgery related risk factors. Intraoperative non-surgery related risk factors for anastomotic healing also contribute to surgical outcome. This review offers an overview of potential modifiable risk factors that may play a role during the operation.

Methods

Two independent literature searches were performed using EMBASE, Pubmed and Cochrane databases. Both clinical and experimental studies published in English from 1985 to August 2015 were included. The main outcome measure was the risk of anastomotic leakage and other postoperative complications during colorectal surgery. Determined risk factors of CAL were stated as strong evidence (level I and II high quality studies), and potential risk factors as either moderate evidence (experimental studies level III), or weak evidence (level IV or V studies).

Results

The final analysis included 117 articles. Independent factors of CAL are diabetes mellitus, hyperglycemia and a high HbA1c, anemia, blood loss, blood transfusions, prolonged operating time, intraoperative events and contamination and a lack of antibiotics. Unequivocal are data on blood pressure, the use of inotropes/ vasopressors, oxygen suppletion, type of analgesia and goal directed fluid therapy. No studies could be found identifying the impact of body core temperature or mean arterial pressure on CAL. Subjective factors such as the surgeons' own assessment

of local perfusion and visibility of the operating field have not been the subject of relevant studies for occurrence in patients with CAL.

Conclusion

Both surgery related and non-surgery related risk factors that can be modified must be identified to improve colorectal care. Surgeons and anesthesiologists should cooperate on these items in their continuous effort to reduce the number of CAL. A registration study determining individual intraoperative risk factors of CAL is currently performed as a multicenter cohort study in the Netherlands.

Introduction

Despite extensive research, the incidence of colorectal anastomotic leakage (CAL) has not decreased (3-19%) over the past decades.[1–3] Research on CAL may focus on the preoperative, intraoperative and postoperative phase.

Research on the *preoperative* period mainly determines patient and surgery related risk factors of CAL. Many of these factors, i.e. age and sex, are non-modifiable. Some are included in the Colon Leakage Score (CLS) that was developed to define the proportion of CAL-risk.[4] The CLS is a list of factors derived from a systematic search that can mainly be consulted prior to colorectal surgery. In addition, prehabilitation programs are being developed to optimize the patient's preoperative condition and nutrition. This promising approach will likely contribute to decrease CAL as many risk factors are related to the patients' lifestyle.[5–8]

Many *intraoperative* surgical risk factors of CAL were subject of research projects. For instance, the role of laparoscopy or stapled anastomosis in right colonic resections was determined. Also the role of a defunctioning stoma for reduction of CAL after rectum resections was proposed.[9,10] However, the importance of many of these findings is still under debate. Non-surgical factors influencing the patients' condition during surgery including anesthesiological techniques might also have a large contribution to the risk of CAL. Recently, a multidisciplinary approach to prevent surgical complications is gaining interest. A combination of interventions was found to reduce the superficial surgical wound infection rate and possibly also CAL.[11] This observation warrants a close(r) collaboration of surgical and anesthesiological teams. Although other intraoperative variables such as operation time, blood loss and blood transfusion requirements have been widely accepted as risk factors, other intraoperative potentially modifiable risk factors are to be discovered yet.

The *postoperative* status of the patient is closely monitored to detect CAL as early as possible.[12] To date, many studies have been performed, and the Enhanced Recovery After Surgery program (ERAS) has been introduced to improve surgical outcome.[13] CAL due to a technical failure will most probably occur within the first few days after surgery. CAL due to other reasons will become evident within 3-6 days post surgery. Consequences of CAL such as peritonitis and intra-abdominal sepsis might be limited if treated promptly. Several studies trying to identify CAL at the earliest stage have met with limited success.[12,14–19] Imaging using radiological techniques has a disappointingly low sensitivity. An evidence-based algorithm is required for early detection of CAL.

Some modifiable risk factors possibly influencing the *perioperative* period such as medication (i.e. corticosteroids and non-steroidal anti-inflammatory drugs), poor nutritional status (i.e. body composition, albumin level) and other lifestyle related factors were not included in this review since these factors are considered as an integrated part of prehabilitation. The present review therefore systematically identified existing and modifiable *intraoperative* risk factors of CAL allowing for recommendations aimed at improving the quality of care for colorectal patients. Collaboration between surgeons and anesthesiologists on improving these items may be the key in the continuous effort to reduce the number of CAL.

Material and methods

A complete search was conducted on August 20th , 2015 using the PubMed version of MEDLINE, the OvidSP version of Embase and the Cochrane library (January 1970 to August 2015). Articles were restricted to the English language. Reference lists were checked for additional studies. Both clinical and experimental studies were included. The main outcome measure was the risk of anastomotic leakage and other postoperative complications during colorectal surgery. Letters and papers omitting CAL as outcome were excluded. Determined risk factors of CAL were stated as strong evidence (level I and II high quality studies), and potential risk factors as either moderate evidence (experimental studies level III), or weak evidence (level IV or V studies).[20]

2.1 Search strategy

Two searches were performed separately by two independent researchers (SJ van Rooijen, D Huisman) with support from the clinical library of Máxima Medical Center (MMC) and VU Medical Center (VUmc). The search headings ‘anastomotic leakage’ and ‘colorectal surgery’ were used in combination with predefined keywords as established by colorectal surgeons of MMC and VUmc (hyperglycemia, glucose level, temperature, anemia, blood loss, tissue oxygen tension, inotropes, vasopressors, blood pressure, mean arterial pressure, hypotension, fluid administration, goal directed therapy, blood transfusion, antibiotics, analgesia, epidural, operation duration, intraoperative events, conversion, contamination and surgical experience; Figure 1). If disagreement existed between the two researchers, a third author (F Daams) aimed at reaching consensus.

Results

The existing evidence regarding intraoperative modifiable parameters was classified into 3 categories, the general status of the patient, tissue perfusion and a surgery related section (table 1).

3.1 General patient status and CAL

Hyperglycemia

Eight studies (human / experimental / retrospective / Cochrane review and 2 recent multicenter RCT's) showed a negative influence of a high preoperative HbA1C on the onset of CAL.[19–26] In general, hyperglycemia is regarded as a predictor of complications of any type in colorectal surgical procedures.[27] Diabetes mellitus, hyperglycemia and a high preoperative HbA1c are all independent risk factors of CAL.[28–35] Risk rates depend on level of hyperglycemia and starts at levels of >140mg/dL with odds ratio's varying from 1.2-4.3. An observational study concluded a higher risk on adverse events due to intraoperative hyperglycemia (>180mg/dL) in non diabetic versus diabetic patients (OR 5.1).[36] However, other observational studies found that non diabetic patients sustained a significantly higher risk of postoperative adverse events compared to diabetic patients, probably as a result of perioperative hyperglycemia.[21–26]

Temperature

Body core temperature below 36 °C beyond 60 minutes induces vasoconstriction and is associated with increased surgical site infection (SSI) rates.[32,37] Unfortunately, no studies indicating the relation of body temperature and CAL were identified. One animal study showed multidirectional changes in perioperative temperature on early stage tissue regeneration after small bowel resection.[38]

3.2 Tissue perfusion and CAL

Blood loss and anemia

Intra-operative blood loss is an important predictor of CAL.[39–41] Even blood loss > 100ml is significantly associated with an increased risk of CAL.[4,42] A ≥50 percent drop or hemoglobin levels <7 g/dL (4.4 mmol/l) following gastrointestinal surgery are predictive of adverse events.[43] A case control study of the Swedish Rectal Cancer registry concluded that severe bleeding was associated with a 1.45 odds ratio of CAL[44], whereas other studies discovered even a higher 3.1-3.32 odds ratio if blood loss was >200ml.[45,46] Severe blood loss causes hypovolemia, tissue hypoxia, and subsequent impaired anastomotic healing.[47,48] As laparoscopic surgery for rectal cancer is associated with attenuated blood loss, this technique appeared beneficial compared to an open approach.[49–52]

Anemia is a risk factor for postoperative myocardial infarction and a potent risk factor for CAL.[39,53–56] Serum hemoglobin <9.4 g/dL (5.9 mmol/l) in the preoperative setting predicted anastomotic leaks.[35,57] One other study demonstrated that perioperative anemia <8g/dl (5mmol/l) was associated with increased postoperative complications and mortality.[58]

Tissue oxygenation

A cohort study found that low tissue oxygen tension was an important deficit leading to wound dehiscence and CAL after colorectal surgery.[59] Three RCT's demonstrated that perioperative supplemented 80% FiO2 during surgery as well as 6 hours postoperatively reduced anastomotic dehiscence.[59–61] Anastomotic leakage was significantly higher in patients with an indexed oxygen delivery of <400 ml/min/m(2).[62] Animal studies reported that tissue oxygen tension was increased by supplemental oxygen[37] and that hyperbaric oxygen enhanced colonic anastomotic healing and anastomotic tissue strength.[63] However, in general, there are deleterious effects described after perioperative high oxygen fractions.[64]

Vasopressors / Inotropes

Literature on the use of vasopressors or inotropes during or after surgery is unequivocal. Two retrospective cohort studies found that the administration of these substances was an independent risk factor for the onset of CAL in 137 and 22 CAL patients, respectively.[39,65] However, small, experimental and retrospective studies demonstrated opposite results.[65,66] Besides, types of vasopressors and inotropes were not always clearly specified.[39]

Blood pressure

A preoperative >90mmHg diastolic blood pressure was associated with a higher risk on CAL as reported in one retrospective study.[67] Preoperative poorly controlled hypertension has a known association with perioperative bradycardia, tachycardia, and hypertension.[68] The duration of severe intraoperative hypotension (51 versus 37 minutes, $P = 0.049$) was also identified as a risk factor of CAL.[39,67] The relation of mean arterial pressure levels (MAP) and CAL has not been described in the literature.

Fluid management

Suboptimal peroperative fluid management might result in CAL and has been shown a risk factor of postoperative complications such as myocardial infarction.[53] Over the years, the necessity of preventing perioperative hypovolemia and – vice versa - fluid overload to prevent perioperative complications became clear.[69,70] Although this consideration primarily led to definition of a liberal or restrictive fluid management, subsequently an individualized perioperative goal-directed fluid management strategy was advised.[71] Aims are to preserve cardiac function and perfusion of vital organs during surgery.[72] Some studies showed reductions in perioperative morbidity and/or mortality using such a goal directed fluid management, especially in high risk abdominal surgical patients.[72–76] Other studies, however, did not demonstrate such differences.[76–78] Despite these controversial results, goal directed therapy (GDT) is considered in ERAS guidelines as beneficial in selected, high risk, cases.[79,80] Benefits of GDT in a high risk abdominal surgical population were reflected in improved postoperative outcome and lower complication rates including surgical site infection according to the NSQIP definition.[73] A moderate grade recommendation of a near-zero fluid balance in low risk patients and low risk surgery (and therefore by definition not in abdominal surgery) was advised.[80] Earlier studies of GDT including one RCT showed marked improvements in morbidity and shortened length of hospital stay (LOS)[81,82] while three other RCT's and retrospective studies did not show any benefits of GDT or amount of infused fluid.[69,77,78,83,84]

Blood transfusion

The requirement of multiple blood transfusions is an independent risk factor of CAL.[85] Four retrospective studies, two prospective studies and a systematic search suggested an association with intraoperative blood transfusion and CAL.[46,85–90] A systematic review also linked intra-operative transfusions and a blood loss >100 mL with increased CAL rates.[89]

3.3 Surgery related issues and CAL

Antibiotics

The combination of intravenous and oral antibiotics decreased the risk of surgical site infections. However, a consequent change in risk of CAL was not observed yet.[91–96] Antibiotic administration between 15-60 minutes before the incision was found to limit the risk of postoperative wound infections.[97]

Analgesia

A retrospective study suggested that the institution of epidural anesthesia did not have with an effect on CAL but may nevertheless be recommended to shorten

LOS.[88] Two systematic reviews and the Swedish rectal cancer registry data reporting on 1474, 4000 and 39.345 patients, respectively demonstrated that epidural analgesia did neither increase CAL rates nor appeared beneficial regarding postoperative outcome.[44,98–101] An experimental dog study showed that epidural analgesia promoted anastomotic healing.[102] Moreover, three retrospective studies found that patients receiving epidural analgesia demonstrated the lowest CAL rate.[103] In contrast, a meta-analysis of 12 small randomized controlled trials suggested that epidurals increase the CAL rate.[104] In conclusion, epidural analgesia or multimodal approach is advised in ERAS guidelines and in general -but not specifically focused on CAL- for open surgery. In contrast, no advise is provided on the use of epidural analgesia in laparoscopic procedures.[80]

Duration of surgery

Prolonged surgery is correlated with higher intra- and postoperative complications. Moreover, an 1.53-9.9 odds ratio of developing CAL was reported.[105–108] A national retrospective cohort including 13.648 patients also concluded that operation time was associated with an increased chance of anastomotic leaks.[109] On the other hand, morbidity and mortality rates were not increased when prolonged laparoscopy operations was compared to open surgery.[110]

Intraoperative events

Intraoperative adverse events such as bleeding complications or iatrogenic injury to solid organs were found to significantly increase the risk of developing CAL.[111] Conversion during colorectal surgery also augmented postoperative morbidity and mortality although the risk of CAL was not affected.[112–115]

Contamination

Several RCT's, meta-analysis, systematic reviews and cohort studies have found that mechanical bowel preparation (MBP) does not influence a risk of colonic anastomotic leakage.[116–126] One RCT and one review revealed that rectal cancer surgery without MBP was associated with a higher postoperative complication rate.[127,128] A combination of MBP and oral antibiotics preparations may decrease morbidity.[129] Moreover, if MBP is combined with oral antibiotics, CAL is reduced by nearly half, as shown in a retrospective review including 8442 patients.[130] Surgery performed in emergency settings without preoperative preparation has an increased risk for anastomotic dehiscence.[131]

Intraoperative contamination or dirty wounds are independent risk factors of anastomotic leakages as demonstrated by a prospective multicenter cohort study.[42] Two retrospective studies and a prospective surveillance also identified intraoperative contamination as a surgery-related risk factor.[85,107,132]

Surgical experience

The surgeon's operative experience has a clear influence on the development of CAL as was recognized in several studies.[46,133,134] A prospective study of 2363 patients also stipulated the importance of the individual surgeon as an independent risk factor of CAL.[135] In contrast, 19 non-randomized observational studies including 14.344 colorectal resections did not identify any differences in CAL between experts and expert supervised trainees.[136] Another observational study revealed that surgical skills, preoperative factors and patient characteristics all equally contributed to the risk of CAL.[137]

Discussion

This literature review provides existing evidence of intraoperative modifiable risk factors of CAL. The exact role of a number of individual intraoperative risk factors of CAL have not always been clearly specified in the past. There is strong evidence to suggest that a large number of intraoperative non-surgical parameters significantly increase the risk of CAL including hyperglycemia, anemia, mistimed or no (suitable) administration of antibiotics, a minimal 100 cc blood loss, blood transfusion, intraoperative events and more than 2 hours of surgery. As a consequence, it is highly important to optimize patients' preoperative status as well as intraoperative status. It is therefore advised to boost hemoglobin levels if lower than 8g/dl (5mmol/l),[138,139] to administer antibiotics between 15 and 60 minutes prior to skin incision,[97,140–143] and to restrict blood loss, intraoperative events and duration of surgery.[111]

Blood glucose levels require intraoperative monitoring whereas hyperglycemia must be corrected preoperatively aiming at a 4.4 to 6.1 mmol/l level.[32,36,140,144–147] A simple finger glucose meter allows for monitoring of diabetic as well as non diabetic patients during the operation. Even the latter category, once hyperglycemic, has a higher risk of postoperative complications and CAL. Iron supplements preoperatively might be the most successful in increasing the hemoglobin concentration, but there is still no major clinical trial to support this finding for patients undergoing colorectal surgery.[148,149] Another option, although more invasive, is to preoperatively supply erythropoietin (EPO). Since one third of patients with a colorectal carcinoma who are candidate for surgery are anemic preoperatively, it is even more important to optimize the hemoglobin level.[150] Accurate administration of intravenous antibiotics prior to surgery has not been directly linked to an decreased risk of CAL, although it lowers postoperative wound infections. However, some studies concluded that the combination of selective digestive decontamination (SDD) and mechanical bowel preparation might lower the risk of CAL. Unfortunately this is not based on the highest levels of evidence and therefore cannot be recommended as standard practice. Operating time and intraoperative adverse events can be limited if the preoperative work up is optimal including the right diagnostics, to have experienced surgeons and operating team, to facilitate optimal surgical conditions, to perform laparoscopic surgery if feasible to limit blood loss and blood transfusions[150] and to limit operations to high volume centers.[151–155]

Considering potential risk factors of CAL, from the present review data on the influence of body core temperature,[156] the role of MAP, blood pressure, inotropes / vasopressors, fluid management, tissue oxygenation and epidural analgesia appeared underexplored. All these factors are anesthesia related potential modifiable risk factors.

Due to heterogeneous methods for intraoperative temperature monitoring combined with surgical setting related difficulties to increase core temperature accurately, it is hard to determine the exact relevance and implications on CAL. Despite the unknown relation of temperature on CAL, a body core temperature of at least 36 degrees is recommended for several reasons (i.e. patient comfort, coagulation, postoperative recovery) and might be achieved with optimal prewarming which starts preoperatively.[157–160]

Perfusion and other hemodynamic parameters of anesthesia perioperatively are mostly modifiable and will possibly be related to the development of CAL. Splanchnic vasoconstriction and subsequent deterioration of microcirculation results in anastomotic hypoxia. Therefore it is recommended to accurately maintain a level of MAP at least greater than 60, since it is considered generally sufficient for providing adequate perfusion pressures to vital organs.[161]

However, we found no direct relation between MAP and CAL. For example, the exact influence of blood pressure on CAL in light of preoperatively poorly regulated blood pressure - possibly resulting in disrupted auto regulation and hypoperfusion due to relative intraoperative hypotension for the new set point – needs to be determined. As well the exact role of auto regulatory blood pressure mechanisms in the pre-existent hypertensic patient in a perioperative setting on risk on CAL needs to be elucidated. Further, the beneficial or harmful effects of using inotropes / vasopressors to optimize blood flow and perfusion pressures and any potential relation towards CAL should be assessed. Beneficial effects might be related to optimizing cardiac output. Harmful effects might be a result of splanchnic vasoconstriction, deterioration of microcirculation resulting in tissue hypoxia. However, until now the underlying mechanism remains unclear.

Over the past years perioperative fluid management has been widely discussed. Present evidence does not allow to give final recommendations on which type of fluid to administer,[162,163] since all types of fluid management have not directly been correlated to the development of CAL. More research is needed to successfully distinguish between the different fluid management options. Until then, GDT (albeit unclear what the exact definition of this strategy is) is recommended in particular for high risk populations. The lower the perioperative risks, the lower the GDT gains are. Fluid overload and mesenteric hypoperfusion caused by hypovolemia have a negative impact on the recovery of bowel function.[76,164] A lower volume status is a potent cause of gut mucosal hypoperfusion, thereby diminishing nutritional support of the tissues at the anastomotic side.

Surgical damage leads to a combination of decreased vascular supply, high cellularity and an increased oxygen demand. With this knowledge supplemental oxygen perioperatively might reduce colorectal anastomotic dehiscence. However, only two RCT’s, one cohort study and two animal studies proved these results. One

pilot study showed that the tissue oxygen saturation (StO2) can be accurately measured with the near-infrared spectroscopy (NIRS). It also revealed that a low StO2 on both sides of the anastomosis is associated with complications.[165] Targeting StO2 optimization did not improve perioperative outcome in a high risk abdominal surgical population.[166] However, especially in critically ill populations arterial hyperoxia is associated with poorer outcomes, although exact cut-off points need to be determined.[167] Moreover, there is debate about the interpretation and conclusion of the results of a recent review in favor of higher inspired oxygen fractions due to heterogeneity issues.[168] Belda et al explained why just increasing perioperative oxygen fractions in order to prevent surgical site infections today seems too short-sighted based on current literature. At last, detrimental effects of perioperative high oxygen fractions might include increased long-term mortality in cancer patients.[64]
For these reasons, the exact role of higher supplemental oxygen delivery in humans in clinical daily practice needs to be determined in much larger study populations. Until then, only preventing perioperative hypoxia remains standard practice.

Epidural analgesia is commonly used in colorectal surgery, but the scientific evidence of the correlation towards CAL remains conflicting. Beneficial effects of epidural analgesia may extend to improved pain control, patient satisfaction and blood oxygenation, a reduced risk of pneumonia and reduced need of prolonged ventilation or reintubation.[169–171] From an anesthesiological perspective, epidural analgesia does not only reduce the postoperative consumption of systemic opioids but directly improves gastrointestinal function and should be considered where possible, at least for open surgical procedures.[172] There is also a low risk of complications due to epidural analgesia.[99] But, if technical failure occurs, the complications can be severe, implying careful assessment for indications.

This review summarizes that certain intraoperative non-surgical risk factors of CAL have been determined and could be optimized pre- and intraoperatively. A ‘bundle of care’ should be introduced including monitoring and adjusting glucose and hemoglobin level, to accurately administer antibiotics prior to surgery and to restrict the amount of blood loss, duration of surgery and intraoperative events by optimizing the operating team and logistics. Unfortunately, still many non-surgical intraoperative parameters remain as undetermined for the risk of developing CAL. This highlights the need to improve collaboration between surgeons and anesthesiologists. It seems rational to improve or optimize patients temperature, fluid status including cardiac output, MAP and vasopressor use intraoperatively, but evidence is still lacking. Therefore, a prospective registration study is recommended to determine the relation of described common practices and factors on CAL and the additional value of such optimization.

Conclusion

Where unchangeable risk factors are used for CAL risk stratification, identification of modifiable risk factors is necessary to substantially reduce the number of CAL and other complications. Both surgical and non-surgical factors will have their contribution on outcome and quality of life. The exact importance of the individual non-surgical intraoperative risk factor is yet to be determined. Surgeons and anesthesiologists should cooperate on these items in the continuous effort to reduce the number of CAL. Therefore, a registration study is recommended and will now be applied by surgeons and anesthesiologists in a multicenter cohort study in the Netherlands, facilitated by the national Taskforce Anastomotic Leakage.

Highlights

Intraoperative risk factors CAL not yet determined. Registration study recommended and started to identify intraoperative modifiable risk factors.

Keywords

Anastomotic leakage, colorectal, surgery, CAL, intraoperative, modifiable, risk factor, anesthesiology

Abbreviations

CAL: Colorectal Anastomotic Leakage

CLS: Colon Leakage Score

MAP: Mean Arterial Pressure

MBP: Mechanical Bowel Preparation

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Appendix III: Intraoperative risk factors table 1 and 2

Table 1. This is an overview of literature on intraoperative modifiable risk factors CAL. Risk factors are categorized into three subgroups: general status, tissue perfusion and surgery related risk factors. Reference numbers are given (…) for each intraoperative modifiable risk factor.

General status	**Tissue perfusion**	**Surgery related**
Hyperglycemia 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35	Blood loss and anemia 4, 34, 38, 39, 40 ,41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57	Antibiotics 90, 91, 92, 93, 94, 95, 96
Temperature 31, 36, 37	Tissue oxygenation 36, 58, 59, 60, 61, 62, 63	Analgesia 43, 79, 87, 97, 98, 99, 100, 101, 102, 103
	Inotropes / Vasopressors 38, 64, 65	Duration of surgery 104, 105, 106, 107, 108, 109
	Blood pressure 38, 66, 67	Intraoperative events 110, 111, 112, 113, 114
	Fluid management 52, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83	Contamination 41, 84, 106, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127 ,128, 129, 130, 131
	Blood transfusion 45, 84, 85, 86, 87, 88, 89	Surgical experience 45, 132, 133 ,134, 135, 136

Table 2. Modifiable intraoperative risk factors CAL as described in the literature. Comment of the authors is based on the existing literature. Strong evidence group includes determined risk factors of CAL based on high quality studies (level I and II), the moderate group includes potential risk factors of CAL based on experimental studies (level III), weak evidence group are potential risk factors of CAL with level IV or V evidence.

Risk factors	**Modifiable**	**Recommendation**	**Comment of the authors***
General status			
Hyperglycemia	+	4,4-6.1 mmol/l	Strong
Temperature	+	> 36°C	Moderate
Local perfusion			
Blood loss and anemia	+	Restrict blood los < 100ml Hemoglobin level > 8 g/dl (>5 mmol/l)	Moderate
Tissue oxygenation	+	Supplemental 80% FiO2 during and 6 hours after surgery	Weak
Inotropes / Vasopressors	+	With caution	Weak
Blood pressure	+	- DBP < 90 mmHg preoperatively. - < 40 % decrease in DBP perioperatively. -MAP >60	Weak
Fluid management Cardiac index	+	- Goal directed therapy for high risk patients. - >2,5 L/min/m2	Weak to Moderate
Blood transfusion	+	No transfusion	Strong
Surgery related			
Antibiotics	+	15-60 min prior to surgery	Moderate
Analgesia	+	According to ERAS guidelines (not specifically focused on CAL)	Weak
Duration of surgery	+	< 2 hours, experienced surgeons	Strong
Intraoperative events	-	No intraoperative events	Strong
Contamination	+	No contamination	Strong
Conversion	+/-	No conversion	Strong
Surgical experience	+	- > 50 surgeries a year - Trained operating team	Moderate

Table 3: Characteristics of 117 included studies. Divided into subcategories. First author of study was depicted including year of study and reference number (…). Design of study, study period, country where the study was performed, number of included patients in case it was not a review and main findings of the studies were additionally highlighted in this table. GDT = goal directed therapy, PGDT = protocol goal directed therapy, LOS = length of hospital stay, CAL = colorectal anastomotic leakage, SSI = surgical site infections, DM = diabetes mellitus, MCG = mean postoperative capillary glucose, BG = blood glucose, BMI = body mass index, SV = stroke volume, RCT = randomized controlled trial, SWI = surgical wound infection, CRC = colorectal cancer, NSQIP = National Surgical Quality Improvement Protocol.

Table 3: Characteristics of 117 included publications, divided into subcategories. First author of study was depicted including year of publication and reference number (…). Design of study, study period, country where the study was performed, number of included patients (not in review articles) and main findings of the studies were additionally highlighted in this table. GDT = goal directed therapy, PGDT = protocol goal directed therapy, LOS = length of hospital stay, CAL = colorectal anastomotic leakage, SSI = surgical site infections, DM = diabetes mellitus, MCG = mean postoperative capillary glucose, BG = blood glucose, BMI = body mass index, SV = stroke volume, RCT = randomized controlled trial, SWI = surgical wound infection, CRC = colorectal cancer, NSQIP = National Surgical Quality Improvement Protocol.

Study	Design	Study period	Country	n	Main findings
Hyperglycemia					
Kiran 2013 (20)	*Observational single center study* on hyperglycaemia during colorectal surgery in non-diabetic patients.	2010-2011	USA	2.628	Postoperative elevated glucose value is adversely associated with morbidity and mortality; this risk is related to the degree of glucose elevation.
Kwon 2013 (21)	*Observational multicenter study* on perioperative hyperglycemia.	2005-2010	USA	11.633	Perioperative hyperglycemia was associated with adverse outcomes in general surgery patients with and without diabetes.
Frisch 2010 (22)	*Observational single center study* on pre- and post surgery blood glucose levels.	1 January 2007 - 30 June 2007	USA	3.184	Perioperative hyperglycemia is associated with increased LOS, hospital complications, and mortality after noncardiac general surgery.
Turina 2006 (23)	*Experimental study and prospective evaluation* of perioperative blood glucose levels.	2004	USA	20 & 5.285	This may provide a mechanism by which high glucose and insulin impair innate immunity.
McConnell 2009 (24)	*Observational study* on colorectal patients.	April 2001 - May 2006	Canada	149	48-h MCG >11.0 mmol/L is independently associated with increased SSI following colorectal resection in patients with DM.
Lee 2014 (25)	*Clinical review.*	Till 2014	USA	-	Further studies are needed.
Jackson 2011 (26)	*Retrospective analysis* of colorectal surgery patients.	2000-2005	USA	9.638	Perioperative BG target of 80 to 120 mg/dL, although avoiding hypoglycemia, might be appropriate.
Lin 2015 (27)	*Meta-analysis* evaluating DM and CAL risk in patients after gastrointestinal resection.	Till 2014	China	-	Perioperative BG target of 80 to 120 mg/dL, although avoiding hypoglycemia, might be appropriate.

Zaharie 2012 (29)	*Retrospective analysis* of colorectal resections.	1996-2005	Romania	1.743	Diabetes is a significant risk factor of CAL.
Gustafsson 2009 (30)	*Observational study* in major colorectal surgery.	November 2005 - March 2007	Sweden	141	HbA1c may identify patients at higher risk of poor glycaemic control and postoperative complications.
Shaffer 2014 (31)	*Retrospective cohort study* of partial or total colon resections.	January 2009 - December 2012	USA	365	Glucose control is a modifiable risk factor of SSI.
Cong 2009 (32)	*Retrospective analysis* of rectal cancer patients who underwent anterior resection.	2005 - 2008	China	738	Diabetes mellitus is a risk factor for anastomotic leakage after rectal surgery.
Volk 2011 (33)	*Retrospective analysis* on perioperative data of colorectal surgery patients and CAL.	2000 - 2007	Germany	463	High BMI, diabetes mellitus, and hypotensive circulation (i.e., shock) upon admission are also strongly correlated to anastomotic leakage.
Ianca 2008 (34)	*Retrospective analysis* on large bowel resection with primary anastomosis.	2002 and 2006	Romania	933	Serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl could be considered as host-related predictive markers for anastomotic leak in large bowel resections for cancer.
Kotagal 2015 (35)	*Retrospective review* in general surgery.	2010–2012	USA	40.836	NDM patients, those with hyperglycemia had significantly higher odds of a composite adverse event.
Temperature					
Shaffer 2014 (31)	*Retrospective cohort study* of partial or total colon resection patients.	January 2009 - December 2012	USA	365	Glucose control is a modifiable risk factor of SSI.
Kimberger 2007 (36)	*Randomized controlled trial* on pigs.	2007	Swiss	16	Supplemental oxygen increased tissue oxygen tension in healthy, peri anastomotic, and anastomotic colon tissue.
Glatz 2014 (37)	*Randomized controlled trial* on rats.	2013	Germany	30	No significant changes were seen in the evaluation of anastomotic stability.
Blood loss and anemia					
Dekker 2011 (4)	*Retrospective cohort study* of left-sided colorectal surgery with primary anastomosis.	2010	Netherlands	121	The CLS can predict the risk of anastomotic leakage following left-sided colorectal surgery.

Lanca 2008 (34)	*Retrospective analysis* on large bowel resection with primary anastomosis.	2002-2006	Romania	933	A serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl could be considered as host-related predictive markers for anastomotic leak in large bowel resections for cancer.
Choudhuri 2013 (38)	*Retrospective analysis* of all anastomotic leakages of colorectal patients.	September 2009 - April 2012	India	1.246	Anemia <8 g/dl was independently associated with increased risk of anastomotic leak.
Bertelsen 2010 (39)	*Prospective cohort study* of patients with colorectal adenocarcinoma.	May 2001 - December 2004	Denmark	1.495	Anastomotic leakage after anterior resection for low rectal tumours is related to the level, male gender, smoking and perioperative bleeding.
Nesbakken 2002 (40)	*Prospective observational study* of colorectal patients.	1983-2000	Norway	393	Multiple regression analysis identified a low anastomosis, major bleeding, and age over 75 years as significant risk factors for the development of anastomotic leaks.
Leichtle 2012 (41)	*Prospective observational study* of colorectal patients.	2007-2010	USA	4.340	Risk factors associated with anastomotic leakage were fecal contamination and intraoperative blood loss of more than 100 mL.
Spolverato 2015 (42)	*Retrospective review of prospectively collected data* on pancreatic, hepatic or colorectal resections.	January 2010 - April 2014	USA	4.669	A Hb level of 50% or greater following gastrointestinal surgery was associated with complications, especially ischemic adverse events, even if the nadir Hb level remained at 7 g/dL or greater.
Jestin 2008 (43)	*Case-control study* of rectal resections.	1995-2000	Sweden	372	Adverse intraoperative events, a long duration of surgery and major bleeding, increase the risk of leakage.
Telem 2010 (44)	*Case-control study* with a prospectively maintained administrative database.	January 2002 - December 2007	USA	180	In patients with IBD, preoperative albumin levels lower than 3.5 g/dL, intraoperative blood loss of 200 mL or more, operative time of 200 minutes or more, and/or intraoperative transfusion requirement increased AL risk.
Tang 2001 (45)	*Prospective single center study* of risk-adjusted surgical outcomes.	February 1995 - December 1998	Taiwan	2.809	In addition to ASA score and surgical wound class, blood transfusion, creation of ostomy, types of operation, use of drainage, sex, and surgeons were important in predicting SSIs after elective

					colorectal resection.
Foster 1985 (46)	*Randomized controlled trial* on rats with colorectal resection.	1984	UK	45	Adequate intra-operative fluid replacement during colonic resection and anastomosis is a prerequisite for successful healing.
Greatorex 1970 (47)	*Retrospective cohort study* on anterior resections and left hemicolectomy.	1957 - 1966	UK	640	It is possible that leakage of anastomosis is related to operative blood loss, and that vasoconstriction produced by haemorrhage has a deleterious effect on the anastomosis.
Zhao 2014 (48)	*Meta-analysis* of 14 randomized controlled trials on laparoscopic versus open surgery in rectal cancer patients.	January 1991 - December 2012	-	-	Compared to the open group, surgical time was prolonged for 31.42 min, the amount of blood loss during the surgery was reduced by 108.95 ml and the proportion of blood transfusion was reduced in the laparoscopic group.
Van der Pas 2013 (50)	*Randomized controlled trial.* Non-inferiority, open-label, comparing open with laparoscopic surgery for rectal cancer patients. COLOR II.	January 2004 - May 2010	Belgium, Canada, Denmark, Germany, the Netherlands, Spain, South Korea, and Sweden	1.044	Laparoscopic surgery was associated with less blood loss, a longer operating time, less use of epidural analgesia, earlier restoration of bowel function, and reduction of the hospital stay.
Kang 2010 (51)	*Randomized controlled trial* comparing open versus laparoscopic surgery after preoperative chemoradiotherapy in patients with mid or low rectal cancer.	April 2006 - August 2009	South Korea	340	Estimated blood loss was less in the laparoscopic group than in the open group, although surgery time was longer in the laparoscopic group.
Hayden et al 2015 (53)	*A retrospective review* was performed on patients who had surgery performed for rectal cancer.	2005-2011	USA	123	Preoperative anemia as possible risk factor for anastomotic leak and neoadjuvant chemoradiation may lead to increased risk of complications overall.
Harju 1988 (54)	*Randomized controlled trial* for iron therapy to improve blood hemoglobin.	1987	Finland	40	Patients with empty iron stores responded well to iron therapy. Not only ferritin ($P<0.001$) but also blood hemoglobin ($P<0.01$) concentrations increased.
Saha 2009 (55)	*Retrospective analysis* on medical, anaesthetic and nursing records.	1999-2005	USA	325	Anemia and hypo-albuminemia may be associated with poor outcome.
Abu-Ghanem 2014	*Prospective data analysis* of patients	2003-2011	Israel	500	Preoperative Charlson score,

(56)	who underwent laparoscopic colorectal surgery.				hemoglobin level, carcinoma, and lower rectum pathologies were found to be independent risk factors for PBT in patients undergoing laparoscopic colorectal surgery.
Dunne 2002 (57)	*Prospective data analysis* (NSQIP) on noncardiac surgical patients.	1995-2000	USA	6.301	High incidence of preoperative en postoperative anemia in surgical patients, with a coincident increase in blood utilization.
Tissue oxygenation					
Kimberger 2007 (36)	*Randomized controlled trial* on pigs.	2007	Swiss	16	Supplemental oxygen increased tissue oxygen tension in healthy, perianastomotic, and anastomotic colon tissue.
Schietroma 2012 (58)	*Randomized controlled trial* on patients with rectal cancer.	February 2008 - February 2011	Italy	72	The overall anastomotic leak rate was 16.6%. 8 patients had an anastomotic dehiscence in the 30% FiO_2 group and 4 in the 80% FiO_2 group ($p < 0.05$). The risk of anastomotic leak was 46% lower in the 80% FiO_2 group vs. the 30% FiO_2.
Schietroma 2014 (59)	*Prospective randomized study* on infraperitoneal anastomosis for rectal cancer.	2008-2013	Italy	81	Supplemental 80% FiO_2 reduced postoperative SSI with few risks to the patient and little associated cost.
Garcia-Botello 2006 (60)	*Randomized controlled trial* on rectal or sigmoid cancer surgery.	June 2003 - January 2005	Spain	45	Perioperative administration of 80% O2 both during surgery and for 6 hours afterwards is associated with an improvement in relative anastomotic hypoperfusion as assessed by the measurement of pHi and PCO2 gap.
Levy 2012 (61)	*Randomized controlled trial* in fluid - optimized patients undergoing laparoscopic colorectal surgery.	2011	UK	75	Anastomotic leakage was significantly higher in patients with a DO_2I of < 400 ml/min/m^2.
Poyrazoglu 2015 (62)	*Randomized controlled trial* on rats.	2013	Turkey	21	The hyperbaric oxygen HBO administration has beneficial effects and contributed to wound healing in colonic anastomosis. Preconditioning-HBO did not alter the results significantly.
Meyhoff 2012 (63)	*Randomized controlled trial* on patients for elective or emergency laparotomy.	October 2006 - October	Denmark	1.386	Administration of 80% oxygen in the perioperative period was associated with significantly increased long-term

		2008			mortality and this appeared to be statistically significant in patients undergoing cancer surgery but not in non cancer patients.
Inotropes					
Choudhuri 2013 (38)	*Retrospective analysis* of all the anastomotic leakages.	September 2009 - April 2012.	India	1.246	Albumin <3.5 g/dl, anemia <8 g/dl, hypotension, use of inotropes, and blood transfusion independently increased the risk of anastomotic leak.
Zakrison 2007 (64)	*Retrospective analysis* of gastro intestinal anastomosis.	January 2000 - April 2004	USA	259	Vasopressors appear to increase anastomotic leaks threefold, independent of clinical/surgical status or hypotension.
Adanir 2010 (65)	*Randomized controlled trial* on rabbits.	2009	New Zealand	42	Vasopressors appeared to increase the risk of anastomotic leakage. BPA was increased with high doses of vasopressor.
Blood pressure					
Post 2012 (66)	*Prospective observational study* on colorectal surgery patients.	-	Netherlands	285	High preoperative diastolic blood pressure and profound intraoperative hypotension combined with complex surgery, marked by a blood loss of ≥250 mL and the occurrence of intraoperative adverse events, is associated with an increased risk of developing anastomotic leakage.
Varon 2008 (67)	*Review* of pharmacologic agents and strategies commonly used in the management of perioperative hypertension.	1992-2007	-	-	The goal of controlling perioperative hypertension is to protect organ function, and is currently recommended based on the assumption that the risk of complications will be reduced and outcomes improved
Fluid management					
Brandstup 2012 (68)	*Randomized controlled trial*, multicenter and double-blinded, in colorectal surgery patients.	March 2008 - July 2009	Denmark	150	No significant differences between the groups were found for overall, major, minor, cardiopulmonary, or tissue-healing complications, neither length of hospital stay.
Brandstup 2006 (69)	*Review* of evidence behind current standard fluid therapy, and analysis of trials examining the effect of fluid	-	Denmark	-	Fluid lost should be replaced, and fluid overload should be avoided.

	therapy on outcome of surgery.				
Holte 2007 (70)	Randomized controlled trial, double blinded, in colonic surgery.	January 2003 - September 2004	USA	32	Despite improvements in pulmonary function and oxygen saturation with a restrictive fluid regimen, overall functional recovery was not dependent on the amount of fluid administered in the fast-track colonic surgery.
Kirov 2010 (71)	Review the perioperative monitoring tools and targets for hemodynamic optimization, assessing the influence of goal-directed therapy in different categories of surgical patients.	-	Israel	-	Based on adequate monitoring, the goal-directed algorithms facilitate early detection of pathophysiological changes and influence the perioperative hemodynamic therapy that can improve the clinical outcome.
Cannesson 2015 (72)	Prospective data analysis on patients undergoing open colectomy, pancreatectomy with cancer, participating in a fluid management protocol (PGDT or no PGDT).	June 2011 - September 2013	USA	320	Fluid balance was not significantly different between the two groups. LOS in the hospital in patients in whom PGDT was not fully reported was 8 (6–11) days compared to 8 (5–11) days in patients in whom PGDT was fully reported ($p = 0.21$).
Futier 2010 (73)	Randomized controlled trial of patients undergoing major abdominal surgery.	May 2008 - December 2008	France	70	Excessive fluid restriction increased the level of hypovolemia, leading to reduced $ScvO_2$ and thereby increased incidence of postoperative complications.
Giglio 2009 (74)	Meta-analysis of the effects of GDT on postoperative GI and liver complications.	Till 2008	-	3.410	GDT, by maintaining an adequate systemic oxygenation, can protect organs particularly at risk of perioperative hypoperfusion and is effective in reducing GI complications.
Bundgaard-Nielsen 2007 (75)	Review of studies in which a goal-directed therapeutic strategy was used in surgical patients.	1966 - October 2006	-	725	GDT with the maximization of flow-related haemodynamic variables reduces hospital stay, PONV and complications, and facilitates faster gastrointestinal functional recovery.
Pestana 2014 (76)	Randomized clinical trial on colorectal surgery patients in 6 tertiary hospitals.	January 2011 - August 2012	Spain, Israel	142	Perioperative hemodynamic protocol guided by a noninvasive cardiac output monitor was not associated with a decrease in the incidence of overall complications or length of stay in major abdominal surgery.

Challand 2012 (77)	*Randomized controlled trial,* double-blinded in major colorectal surgery.	March 2009 - April 2010	UK	179	Intraoperative SV optimization conferred no additional benefit over standard fluid therapy.
Knott 2012 (78)	*Delphi analysis* using three rounds of reiterative questionnaires to obtain consensus.	May 2010 - July 2010	UK	86	Agreement was reached on the role of regional analgesia and the use of esophageal Doppler for intraoperative GDT.
Feldheiser 2015 (79)	*Consensus review* including meta-analyses, randomized controlled trials and large prospective cohort studies.	1966-2014	-	-	This consensus statement demonstrates that anesthesiologists control several preoperative, intraoperative and postoperative ERAS elements.
Gómez-Izquierdo 2015 (80)	*Meta analysis* of randomized clinical trials and cohort studies.	January 1989 - June 2013	-	1.399	GDT facilitated the recovery of bowel function, particularly in patients not treated within enhanced recovery programmes and in those undergoing colorectal operations.
Funk 2015 (81)	*Randomized controlled trial* in elective open repair of abdominal aortic aneurysm.	2014	Canada	40	Despite being associated with fewer complications and improved hemodynamics, there was no difference in the inflammatory response of patients treated with GDT.
Phan 2014 (82)	*Randomized controlled trial* on fluid restriction.	2012-2013	Australia	100	The increased perioperative fluid volumes and increased stroke volumes at the end of surgery in patients receiving GDT did not translate to a significant difference in LOS or complications.
Von Heymann 2006 (83)	*Retrospective analysis* of colonic surgery.	2001-2005	Germany	136	The incidence of postoperative complications was not different between patients who were infused 36ml/kg or 53ml/kg of fluids during surgery and post anesthesia care unite stay.
Blood transfusion					
Tang 2001 (45)	*Prospective single center study* of risk-adjusted surgical outcomes.	February 1995 - December 1998	Taiwan	2.809	In addition to ASA score and surgical wound class, blood transfusion, creation of ostomy, types of operation, use of drainage, sex, and surgeons were important in predicting SSIs after elective colorectal resection.

Makela 2003 (84)	*Case control study* on reoperated patients for colorectal anastomosis leakage.	1992-2001	Finland	88	Patients with multiple risk factors have higher risk for anastomotic leakage. When patients have three or more risk factors, the creation of a protective stoma should be considered in cases with a low rectal anastomosis.
Alves 2002 (85)	*Retrospective review* of colorectal resections.	1990-1997	France	707	Blood transfusion intra-operatively is associated with CAL.
Park 2013 (86)	*Retrospective analysis* of patients with rectal cancer.	January 2006 - March 2009	Korea	1.609	Male sex, low anastomosis, preoperative chemoradiation, advanced tumor stage, perioperative bleeding, and multiple firings of the linear stapler increased the risk of CAL after laparoscopic surgery for rectal cancer.
Lai 2013 (87)	*Retrospective study* on colorectal patients.	2000-2011	China	1.312	ASA score, history of hypertension, episodes of hypotension, anastomosis technique, tumor localization, anesthesia duration, and perioperative blood transfusion were significant risk factors for CAL.
Qu 2015 (88)	*Systematic review* on cohort, case–control studies, and randomized controlled trials that examined clinical risk factors for CAL.	Till August 2014	-	4.580	Four operative factors were significantly associated with increased risk of CAL: including longer operative time, number of stapler firings ≥3, intra-operative transfusions/blood loss >100 mL, and anastomosis level within 5 cm from the anal verge.
Boccola 2011 (89)	*Prospective analysis* of patients with colorectal anastomosis.	1984-2004	Australia	1.576	Significant risk factors were anterior resection, anastomosis using an intraluminal stapling device, abdominal drain via laparoscopic port, postoperative blood transfusion, primary cancer site at the rectum, and TNM stage of T2 or higher. Having an LEK showed significant impact on overall, cancer-related, and disease-free survival.
Antibiotics					
Sadahiro 2014 (90)	*Randomized controlled trial* on the effectiveness of oral antibiotics and probiotics in preventing postoperative	2008-2011	Japan	300	Recommend oral antibiotics, rather than probiotics, as bowel preparation for elective colon cancer procedures

	infection in elective colon cancer procedures.				to prevent surgical-site infections.
Abis 2013 (91)	*Review* on studies of selective decontamination of the digestive tract.	1970-2012	Netherlands	-	On the basis of available evidence, the authors have now instigated a large multicenter RCT to evaluate the role of SDD in colorectal cancer surgery on anastomotic leakage (SELECT trial).
Abis 2013 (92)	*Randomized multicenter study* comparing preoperative SDD combined with standard antibiotic prophylaxis with standard antibiotic prophylaxis alone in elective CRC surgery patients.	Till 2013	Netherlands	762	Selective decontamination of the digestive tract will reduce clinical CAL, thereby reducing the morbidity and the mortality in CRC patients.
Kobayashi 2014 (93)	*Prospectively data analysis* on patients undergoing colorectal resection.	2002-2010	Japan	918	In patients with anastomotic leakage after surgery, the empirical use of antimicrobial regimens with broad-spectrum activity against both aerobic and anaerobic organisms to treat postoperative intra-abdominal infections following colorectal surgery in accordance with the 2010 IDSA/SIS guidelines is associated with better outcomes.
Rowe-Jones 1990 (95)	*Randomized controlled trial* comparing two prophylactic antibiotic regimens in a parallel group trial.	1987-1989	UK	1.018	A single preoperative dose of cefotaxime plus metronidazole is as efficacious as a three dose regimen of cefuroxime plus metronidazole in preventing wound infection after colorectal surgery and has practical advantages in eliminating the need for postoperative antibiotics.
Nelson 2009 (96)	*Retrospective analysis* to investigate the single, dichotomous outcome of SWI.	-	-	30.880	Antibiotics delivered will reduce the risk of postoperative SWI by at least 75%.
Analgesia					
Jestin 2008 (43)	*Case-control study,* data from the Swedish Rectal Cancer Registry were analysed.	1995-2000	Sweden	402	Except for a protective stoma, none of the variables considered as possible targets for improvement (postoperative epidural anaesthesia, observation at intensive care unit for more than 24 h, and intra abdominal drainage) proved to be protective factors.

Feldheiser 2015 (79)	*Consensus review* including meta-analyses, randomized controlled trials and large prospective cohort studies.	1966-2014	-	-	This consensus statement demonstrates that anesthesiologists control several preoperative, intraoperative and postoperative ERAS elements.
Lai 2013 (87)	*Retrospective study* on the risk of anastomotic leakage in colorectal surgery patients.	2000-2011	China	1.312	ASA score, history of hypertension, episodes of hypotension, anastomosis technique, tumor localization, anesthesia duration, and perioperative blood transfusion were significant risk factors for AL.
Popping 2014 (97)	*Systematic Review and Meta-analysis* of randomized controlled trials.	Till July 2012	-	9.044	In adults having surgery under general anesthesia, concomitant epidural analgesia reduces postoperative mortality and improves a multitude of cardiovascular, respiratory, and gastrointestinal morbidity endpoints compared with patients receiving systemic analgesia.
Halabi 2014 (98)	*Retrospective review* of laparoscopic colorectal cases performed with or without epidural analgesia for cancer, diverticular disease, and benign polyps.	January 2002 - December 2010	USA	191.576	Epidural analgesia did not affect the incidence of respiratory failure, pneumonia, anastomotic leak, ileus, or urinary retention.
Halabi 2013 (99)	*Retrospective analysis* on nationwide inpatient sample for elective open colorectal surgeries performed for benign and malignant conditions with or without the use of epidural analgesia.	2002–2010	USA	888.135	Epidural analgesia in open colorectal surgery is safe but does not add major clinical benefits over conventional analgesia.
Piccioni 2015 (100)	*Retrospective study* on colorectal cancer patients and the risk of anastomotic leakage.	May 2008 - December 2011	Italy	1.474	Epidural analgesia does not influence the AL risk after open colorectal surgery for cancer.
Blass 1987 (101)	*Randomized controlled trial* on dogs.	1986	USA	16	Intraoperatively, the epidural-general anesthesia dogs tended to bleed less, making the anastomosis less difficult.
Ryan 1989 (102)	*Three retrospective studies* were conducted to compare the outcomes of colorectal anastomoses, with and without resections, with respect to anaesthetic technique.	1987	Germany	-	Anastomotic leak rates and death rates were lower in the CRAG group, and the lowest incidence of anastomotic leak was reported in the patients receiving CEA.
Holte 2001 (103)	*Review* of randomized controlled trials aiming to investigate	1966-May 2000	-	562	There is no statistically significant evidence from randomized controlled

	postoperative outcome.				trials to indicate epidural analgesia with local anaesthetic to be associated with an increased risk of anastomotic breakdown.
Duration of surgery					
Suding 2008 (104)	*Prospective review* of patient and operative characteristics that contribute to anastomotic leaks.	May 2002 - March 2005	USA	672	Significant risk factors for anastomotic leaks include low preoperative serum albumin level, steroid use, male sex, and increased duration of surgery.
Lipska 2006 (105)	*Review* of the anastomotic leakage rates in a single colorectal Unit to evaluate the risk factors for anastomotic leakage after lower gastrointestinal anastomosis.	1999-2004	New Zealand	541	Male gender, previous abdominal surgery and low rectal cancer are associated with increased anastomotic leakage rates.
Konishi 2006 (106)	*Prospective surveillance* of all elective colorectal resections performed by a single surgeon in a single university.	November 2000 - July 2004	Japan	391	Preoperative steroid use, longer duration of operation, and contamination of the operative field were independent risk factors for developing clinical anastomotic leakage after elective resection for colorectal cancer.
Gervaz 2012 (107)	*Multicenter prospective surveillance program* to assess the incidence of SSI.	October 2008 - November 2010	Switzerland	534	A simple clinical score based on four preoperative variables was clinically useful in predicting the risk of SSI in patients undergoing colorectal surgery.
Midura 2015 (108)	*Retrospective analysis* of patients who underwent segmental colectomy with anastomosis.	2012	USA	13.684	Male sex, steroid use, smoking, open approach, operative time, LOS, 30-day mortality, and preoperative chemotherapy were associated with increased anastomotic leaks and diverting ileostomy with decreased incidence of leaks on multivariate analysis.
Buunen 2009 (109)	*Randomized controlled trial* in 29 European hospitals on patients with solitary cancer of the colon and a body-mass index up to 30 kg/m^2, randomly assigned to either laparoscopic or open surgery as curative treatment.	March 1997 – March 2003	Europe	1.248	The difference in disease-free survival between groups was small and, we believe, clinically acceptable, justifying the implementation of laparoscopic surgery into daily practice.
Intraoperative events					
Kambakamba 2014 (110)	*Retrospective analysis* of elective laparoscopic colorectal resection based on the prospective database of the Swiss Association of Laparoscopic and Thoracoscopic Surgery.	1995-2006	Switzerland	3.928	Patients with an intraoperative adverse event had a significantly higher rate of postoperative local and general morbidity (41.2 and 32.9 % vs. 18.0 and 17.2 %, $p < 0.001$ and $p < 0.001$, respectively).
Goriainov 2008 (111)	*Prospective audit* of all patients undergoing laparoscopic surgery.	January 2003 - August 2006	UK	84	The anastomotic leak rate from intra-corporeal laparoscopic anastomosis is no greater than for open surgery or laparoscopic surgery with extra-corporeal

					anastomosis.
Casillas 2004 (112)	*Case-Control study* on colectomies.	January 1999 - August 2002	USA	430	Conversion of a laparoscopic colectomy does not result in inappropriately prolonged operative times, increased morbidity or length of stay, increased direct costs, or unexpected readmissions compared with similarly complex laparotomies.
Marusch 2001 (113)	*Multicentric, prospective, observational study* within the Laparoscopic Colorectal Surgery Study Group.	August 1995 - February 1999	Germany, Switzerland, Austria	1.658	Conversion is not considered to be a complication of laparoscopic surgery, it is true that the postoperative course after conversion is associated with appreciably poorer results in terms of morbidity, mortality, convalescence, blood transfusion requirement, and postoperative hospital stay.
Kuhry 2005 (114)	*Randomized clinical trial* including patients with colon cancer undergoing either laparoscopic or open operation.	March 1997 - March 2003	Europe	536	Laparoscopic operation for colon cancer at hospitals with high caseloads appears to be associated with improved short-term results.
Contamination					
Leichtle 2012 (41)	*Prospective observational study* of colorectal patients.	2007-2010	USA	4.340	Risk factors associated with anastomotic leakage were fecal contamination and intraoperative blood loss of more than 100 mL.
Makela 2003 (84)	*Case control study* on reoperated patients for colorectal anastomosis leakage.	1992-2001	Finland	88	Patients with multiple risk factors have higher risk for anastomotic leakage. When patients have three or more risk factors, the creation of a protective stoma should be considered in cases with a low rectal anastomosis.
Konishi 2006 (106)	*Prospective surveillance* of all elective colorectal resections performed by a single surgeon in a single university.	November 2000 - July 2004	Japan	391	Preoperative steroid use, longer duration of operation, and contamination of the operative field were independent risk factors for developing clinical anastomotic leakage after elective resection for colorectal cancer.
Ahmad 2003 (115)	*A descriptive, analytical and observational study* on colorectal surgery and MBP.	September 1998 - April 2003	Pakistan	47	Mechanical bowel preparation is not necessary for safe colorectal surgery.
Cao 2012 (116)	*Systematic review* including 14 randomized clinical trials comparing MBP with no MBP before colorectal	1992-2010	-	5.373	No evidence was noted supporting the use of MBP in patients undergoing elective colorectal

	surgery.				surgery. MBP should be omitted in routine clinical practice.
De Aguilar-Nascimento 2009 (117)	*Prospective cohort study* on patients who underwent bowel surgery with an anastomosis.	2004-2008	Brazil	53	The multidisciplinary routines of the ACERTO protocol are safe and enhanced recovery in colorectal surgery by reducing both hospitalization and the severity of postoperative morbidity.
Gravante 2008 (118)	*Meta-analysis* of 12 randomized controlled trials.	Till 2007	-	4.919	Compared with mechanical bowel preparation, non-mechanical bowel preparation for colorectal surgery was associated with a non-significant difference in the rate of anastomotic leakage.
Guenaga 2003 (119)	*Meta-analysis* of 6 randomized controlled trials.	Till 2002	-	1.159	The results failed to support the hypothesis that bowel preparation reduces anastomotic leak rates and other complications.
Kovachev 1998 (120)	*Prospective cohort study* on colorectal surgery patients and the use of antibiotic prophylaxis.	1997	Bulgaria	136	In colorectal operations antibacterial prophylaxis applied perioperatively proves effective in combating systemic and local inflammatory complications.
Lins-Neto 2012 (121)	*Prospective cohort study* of patients undergoing abdominal surgery without prior bowel preparation.	January 2007 - June 2011	Brazil	126	Preoperative mechanical bowel preparation is not essential in the routine of colorectal surgeries.
Pineda 2008 (122)	*Meta-analysis* of thirteen randomized controlled trials of colorectal cancer patients and MBP.	1992-2008	UK	4.601	MBP is of no benefit to patients undergoing elective colorectal resection and need not be recommended to meet "standard of care."
Pirro 2006 (123)	*Comparative study* of MBP in colorectal surgery.	2001-2004	France	190	Colorectal surgery without MBP may be safely performed and could improve the quality of life of patients in the peri-operatory period.
Young Tabusso 2002 (124)	*Prospective cohort study* of MBP in colorectal surgery.	2001	Spain	47	The results show that mechanical preparation of the colon does not provide any benefit and may result in a higher incidence of complications in colorectal surgery.
Nasirkhan 2006 (125)	*Review* of anastomotic disruption after large bowel resection.	1953-2005	-	-	Male gender, obesity, level of anastomosis, peritoneal contamination, age, operative time and blood transfusions, have all been implicated as potential risk

					factors for CAL.
Kim 2014 (126)	_Retrospective analysis_ of prospectively collected data in colorectal surgery.	September 2010 - August 2012	Korea	380	Colon cancer surgery can be performed safely without an MBP with respect to anastomosis leakage, SSI and the severity of surgical complication.
Muller-Stich 2006 (127)	_Systematic review_ of 10 RCT and 7 meta-analyses comparing orthograde bowel cleansing to no preoperative bowel preparation.	-	-	-	Routine preoperative orthograde bowel cleansing is no longer justified prior to colorectal surgery in general due to increased risk of anastomotic leakages.
Moghadamyeghaneh 2015 (128)	_Retrospective analysis_ of the NSQIP database to examine the clinical data of colon cancer patients undergoing scheduled colon resection.	2012-2013	USA	5.021	Solitary mechanical bowel preparation and solitary oral bowel preparation had no significant effects on major postoperative complications after colon cancer resection. However, a combination of mechanical and oral antibiotic preparations showed a significant decrease in postoperative morbidity.
Kiran 2015 (129)	_Retrospective analysis_ of the NSQIP colectomy data.	2012	USA	8.442	On multivariable analysis, MBP with antibiotics, but not without, was independently associated with reduced anastomotic leak, SSI, and postoperative ileus.
Calin 2013 (130)	_Prospective study_ to determine risk factors for anastomotic leak colorectal cancer excision, and to determine the predictive value in a single center.	2006-2010	Romania	251	Surgery performed in emergency settings, on debilitated patients without adequate preoperative preparation, has an increased risk for anastomotic dehiscence.
Asteria 2008 (131)	_Retrospective survey_ identifying risk factors of CAL.	January 2015 - December 2005	Italy	520	Identified several risk factors for CAL.
Surgical experience					
Tang 2001 (45)	_Prospective single center study_ of risk-adjusted surgical outcomes.	February 1995 - December 1998	Taiwan	2.809	In addition to ASA score and surgical wound class, blood transfusion, creation of ostomy, types of operation, use of drainage, sex, and surgeons were important in predicting SSIs after elective colorectal resection.
Manilich 2013 (132)	_Retrospective analysis_ on prospective collected data from the departmental	2010-2011	USA	3.552	Body mass index, operative time, and the surgeon who performed the operation

	outcomes database of colorectal surgery.				are the 3 most important factors influencing readmission rates, rates of transfusions, and surgical site infection.
Biondo 2010 (133)	*Observational study* on emergency colorectal resection.	January 1993 - December 2006	Spain	1.046	Specialization in colorectal surgery has a significant influence on morbidity, mortality, and anastomotic dehiscence after emergency operations.
Damen 2014 (134)	*Prospective evaluation* was performed on patients undergoing bowel surgery within a colorectal surgical unit.	1996-2012	Australia	2.263	Majority of predictors for anastomotic leak were fairly intuitive. The individual surgeon is an independent predictor for leaks.
Kelly 2014 (135)	*Meta-analysis* including 19 non-randomized, observational studies.	1980-2013	-	14.344	In selected patients, it is appropriate for supervised trainees to perform colorectal resection.
Birkmeyer 2003 (136)	*Prospective analysis* of patients undergoing one of the eight cardiac procedures or cancer resections.	1998-1999	UK	474.108	Patients can often improve their chances of survival substantially, even at high-volume hospitals, by selecting surgeons who perform the operations frequently.

Appendix II: Flow Diagram

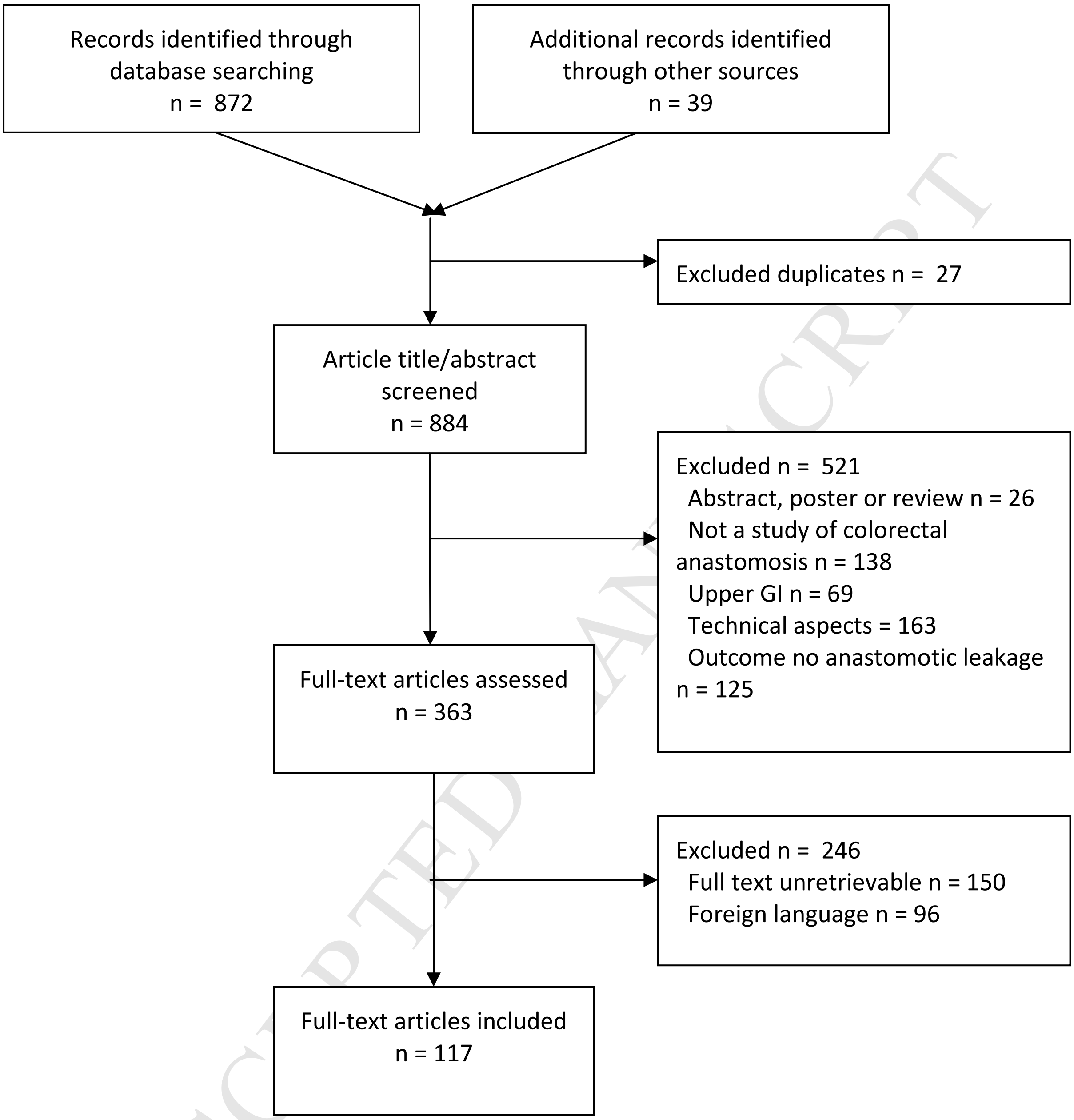

Figure 1. Flow diagram of study selection.

Highlights

INTRAOPERATIVE MODIFIABLE RISK FACTORS OF COLORECTAL ANASTOMOTIC LEAKAGE

WHY SURGEONS AND ANESTHESIOLOGISTS SHOULD ACT TOGETHER

1. There are many intraoperative risk factors of CAL which are modifiable by improvements in perioperative care.
2. Many studies performed, however data not always univocal. Multicenter registration study is necessary to determine the exact contribution of each intraoperative factor in development of CAL.
3. Temperature <36 degrees Celsius, perioperative anemia, intraoperative blood loss and transfusion, duration of surgery, intraoperative events and contamination are all modifiable risk factors of CAL.
4. Even in non-diabetes patients perioperative hyperglycemia increases the risk of CAL.