

Special Article – Colorectal Surgery

Sepsis Prevention in Colorectal Surgery: Is Patient Factor More Important than Surgeon Factor?

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Abstract

Postoperative infection is an important complication of colorectal surgery and continued efforts are needed to minimize the risk of Surgical Site Infection (SSI). Sepsis prevention in colorectal surgery depends upon (a) the degree of contamination of the peritoneal cavity (*disease factor*), (b) the preoperative status of the patient (*patient factor*) and (c) surgical technique (*surgeon factor*). Inter-individual variation in the pattern of mediator release and of end-organ responsiveness may play a significant role in determining the initial physiological response to major sepsis and this in turn may be a key determinant of outcome. Immune response and metabolic regulation are highly integrated as minor operations may stimulate the immune response but the effect of major surgery is immunosuppression. The review elucidates the relative contributions and impact of patient and surgeon-related factors on sepsis prevention in colorectal surgery. The most important prognostic factors in emergency colorectal surgery are the preoperative status: (a) age and (b) faecal peritonitis. Together the mortality is greater than 60% and co-morbidity accentuated the morbidity and mortality from sepsis. The patient factor is more important than the surgeon factor in the prognosis of sepsis in emergency colorectal surgery but, the surgeon factor remains the single most important factor that can influence the morbidity and mortality from sepsis in both elective and emergency colorectal surgery.

Keywords: Colorectal; Surgery; Sepsis; Patient; Disease

Introduction

Intra-abdominal sepsis is one of the most challenging situations in surgery [1]. Colorectal surgery is associated with a high sepsis rate which may lead to serious complications including death. According to the CDC National Nosocomial Infection Surveillance (NNIS) risk index that applies a range from 0-3 points for the absence or presence of the following three composite variables: *1point* - the patient that has an operation classified as either contaminated or dirty; *1point* - the American Society of Anaesthesiologists (ASA) pre-op assessment score of 3, 4, 5 and *1point* - the duration of operation exceeds the 75th percentile of operation time) colon surgery carries the highest risk of Surgical Site Infection (SSI) followed by vascular surgery, cholecystectomy and organ transplant [2]. Postoperative infection is an important complication of colorectal surgery and continued efforts are needed to minimize the risk of Surgical Site Infection (SSI). SSI may be superficial incisional infection involving the subcutaneous tissue, deep incisional infection involving the deep soft tissue or organ/space surgical site infection. Dirty/ contaminated surgery would render a SSI risk of > 50%. SSIs results in 10 billion dollars in cost/year in USA [3]. The patient with an SSI stays hospitalized 7 days longer, is 60% more likely to spend time in the ICU, is 5 times more likely to be readmitted within 30 days of discharge and is twice as likely to die [4]. Despite the major impact of prophylactic antibiotics, the overall incidence of sepsis after elective surgery remains static (5-10%) [1]. Though technical factors may play a part this residual sepsis may be a reflection of perturbation of the immune system due to surgical stress [5].

Discussion

Intra-abdominal sepsis in colorectal surgery

Intra-abdominal sepsis may be spontaneous (at the time of the colorectal catastrophe) or postoperative. The former may be due to colonic or rectal perforation with a wide aetiology. The latter may be due to an anastomotic leak, inadequate elimination of sepsis, an unrecognised perforation or an infected haematoma. Sepsis prevention in colorectal surgery depends upon (1) the degree of contamination of the peritoneal cavity (*disease factor*), (2) the preoperative status of the patient (*patient factor*) and (3) surgical technique (*surgeon factor*) [6,7]. Thus, the complex interactions between the surgeon, patient and disease (Figure 1). A reported 12-fold variation in the 30-day mortality rate following emergency abdominal surgery in 21st century Britain ranged from 3.6% in the best performing hospital to 41.7% in the worst [8]. This would be alarming in the developing world where a < 17 % mortality was reported in Kigali, Rwanda where emergency abdominal surgery was performed in < 24h of admission, guided by the Mannheim peritonitis index score [9]. This shows that surgical outcome depends on a complex interaction of many factors (surgeon, anaesthetist, patient, disease, demography and success is obtained with the early onset of specific therapeutic procedures in the best hospitals [8].

Surgeon factor

The most important factor in determining postoperative sepsis is the presence of viable organisms in the surgical field prior to wound closure. Despite antibiotic prophylaxis and therapy surgeon factor (decision- making and surgical technique) remain the single most

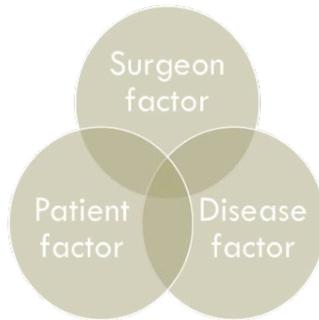


Figure 1: Schematic diagram of the interaction between surgeon, patient and disease factors.

important factor that can influence the morbidity and mortality from sepsis in colorectal surgery. Decisions about surgery in the emergency setting are made on an individual basis. This include damage- control surgery approach for intra-abdominal sepsis- acute resection of sepsis, drainage, and delayed reconstruction at re-look laparotomy at 48h after correction of physiology [10], avoiding anastomosis after resection by exteriorising the bowel ends as stomas, or a Hartmann's procedure for a 'L' sided colonic/ rectal sepsis or perforation. A laparostomy may be required if there is risk of developing abdominal compartment syndrome from severe sepsis and septic shock [11,12]. In a less severe situation, the intraoperative irrigation of the colon may permit primary colorectal anastomosis [6,7,11]. Surgical techniques include anastomotic technique and intraoperative measures to prevent sepsis in colorectal surgery [6]. The measures include intraoperative air-testing of colorectal anastomosis [13], fluorescence imaging of the microcirculation of the anastomosis and the creation of a defunctioning loop ileostomy for high risk colorectal anastomosis [6,14]. Proximal faecal diversion does not decrease the rate of anastomotic leak, but has been shown to decrease mortality and septic complications in those patients who do leak [15-17]. The risks to health and subsequent function from an unprotected anastomotic leak occurring in 10-20% of ultra-low anastomosis are such that a stoma should be employed in all cases [17]. A combination of anatomical inaccessibility, less than optimal blood supply, tightly closed anal sphincters below an ultralow anastomosis and an infected pelvic haematoma are likely to be contributory to anastomotic leakage. Thus, there is the potential role of a transanal drainage tube in the reduction of the endoluminal pressure as well as faecal diversion resulting in a protective effect on anastomotic healing. The current vogue of placing a transanal drainage tube in patients with colorectal anastomoses is safe, simple and claims to reduce the rate and severity of anastomotic leakage [18]. However, there has only been one prospective randomized controlled study that demonstrated this benefit [19]. By avoiding hypotension, hypoxia and hypothermia, optimal perioperative anaesthetic care would allow primary resection and anastomosis in the emergency setting and promote anastomotic healing in the critical first 48 h after surgery [20,21]. The acute onset of abdominal pain and generalized peritonitis is a serious manifestation of an anastomotic leak and these patients may quickly progress to septic shock, requiring intensive care monitoring and resuscitation with fluids and inotropic agents [22]. Patients with diffuse peritonitis from an anastomotic leak or perforated viscus cannot be fully resuscitated until ongoing soiling has been controlled [10,23,24].

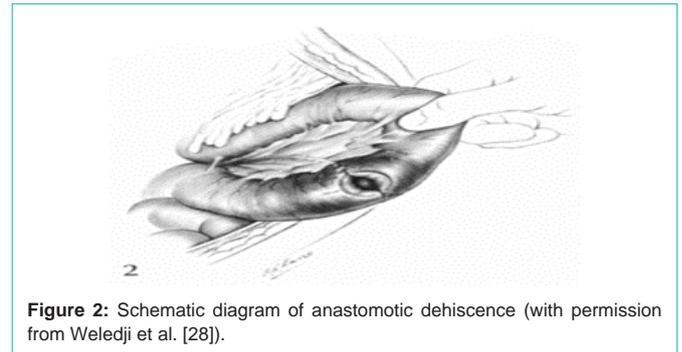


Figure 2: Schematic diagram of anastomotic dehiscence (with permission from Weledji et al. [28]).

Anastomotic leakage: Anastomotic leak is an independent predictor of mortality (40%) due to sepsis, higher than any natural condition and, delayed diagnosis worsens the prognosis [24-26] (Figure 2). It may be early (3-5 days post operation) as a result of technical failure (*surgeon factor*), or more commonly late (weeks) as a result of tissue (biological) failure due to ischaemia, tissue quality or sepsis (*patient, surgeon factor or both*) [27]. The surgeon may have poorly judged the viability of the bowel ends or more commonly overzealously 'cleaned' the bowel ends thus hampering the microcirculation. The pathogenesis of anastomotic leak is however multifactorial as the reported leak rate ranges widely between 3% and 22% [24-28]. These include surgical technique, impaired microcirculation, life-style related factors (smoking, alcohol abuse) and post- operative Non-Steroidal Anti-Inflammatory Drugs (NSAIDS).

NSAIDS and anastomotic leakage: NSAIDS have been widely used in colorectal surgery due to their opioid-sparing effects. Following their study on rats showing an increased risk of anastomotic leakage, Klein et al. in 2012 [29] recommended that NSAIDS be abandoned after primary resection and anastomosis because of effects on collagen metabolism. Several clinical studies have since indicated an increased risk of anastomotic leakage following NSAID treatment although conflicting results exist and a well-powered randomized clinical trial is warranted. A more recent meta-analysis by Peng et al. [30] demonstrated that post-operative NSAIDS, especially non-selective NSAIDS could increase the incidence of anastomotic leak. Haddadd et al. [31] reported NSAIDS being safe in emergency general surgery patients undergoing small bowel resection and anastomosis. They advised its cautious use in emergency general surgery patients with colon or rectal anatomises. Fjedeholt et al. [32] found a strong association between the postoperative use of NSAIDS and the risk for anastomotic leakage after surgery for gastro-esophageal junction cancers. A most recent study reported postoperative NSAID treatment being safe and does not seem to increase the risk of symptomatic anastomotic leakage after anterior resection for rectal cancer [33].

Post- operative intra-abdominal sepsis: This may be due to anastomotic leak with localised sepsis or commonly due to the inadequate elimination of sepsis especially following generalized faecal peritonitis [34]. The main sites of intra-abdominal abscess are usually over the site of the origin of infection or in the dependent areas of the body: subphrenic spaces, pelvis (pouch of Douglas), hepatorenal (Morrison's) pouch, paracolic gutters and the lesser sac. Clinical suspicion of a post- operative intra-abdominal abscess will include a swinging pyrexia, increasing pain, pulse and mass

[1,35]. Unlike generalized peritonitis which demands emergency laparotomy, intra-abdominal abscess must be treated urgently, not emergently. Drainage should be performed within 12 h of diagnosis, but, patients critically ill with a severe systemic septic response require immediate drainage following initial haemodynamic and respiratory resuscitation [35,36]. CT or Ultrasound – guided percutaneous drainage of abdominal abscesses has emerged as the procedure of choice in many circumstances as morbidity and mortality is lower than following operative drainage [37]. Operative drainage is necessary for those abdominal abscesses which are multiple, are isolated but cannot safely be approached percutaneously, and/or are associated with systemic sepsis unresponsive to percutaneous drainage [24,37]. The mortality from postoperative intra-abdominal abscess is greater than 50% and the mortality increases with each operation to treat recurrent or persistent sepsis [24]. This is due to the deteriorating septic state of the patient superimposed on the stress of surgery and, the increased dissection required by re-operative surgery with increased risk of injury and ischaemia to tissues [24,38]. Therefore, the best opportunity to eradicate infection is the first operation.

Disease factor

Sepsis prevention in colorectal surgery depends upon whether it is elective (planned) or emergency surgery. Elective surgery is clean-contaminated and mortality from sepsis is less than 1%. In emergency surgery there is imminent or frank faecal contamination and the mortality may be greater than 50% [6,7]. The high mortality is due to (a) faecal peritonitis, (b) inadequate preoperative optimization, (c) advanced nature of the disease, and (d) patient related factors (comorbidity). According to the 'recommendations for best practice' from the Association of coloproctology of UK and Ireland, and the Scottish intercollegiate Guidelines Network, surgeons should expect to achieve an operative mortality of less than 20% for emergency surgery and 5% for elective surgery for cancer; an overall leak rate below 4% for colonic resection, and wound infection rates after surgery for colorectal cancer should be less than 10% [15]. Although prophylactic antibiotic therapy is inferior to good surgical and aseptic technique, patient mortality is significantly lower when appropriate antibiotics are prescribed early in the course of sepsis (early goal-directed therapy) [39]. Several scoring systems using haematological, biochemical and clinical variables offer comparative indices of disease severity but limited individual prognostic use. The Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM) score is used in wards and the High Dependency Unit (HDU) and may be an admission criteria to HDU or the Intensive Care Unit (ICU) [40]. The Acute Physiology, Age and Chronic Health Care Evaluation (APACHE-II) score of >8 predicts a 15-18% mortality [41], and the acute phase protein, C-Reactive Protein (CRP) of < 125mg/dl is a good negative predictive value for postoperative intra-abdominal sepsis [42]. Thus these scoring systems may influence surgical decision-making and procedure. The Mannheim Peritonitis Index (MPI) is a good predictor of peritonitis outcome and risk of death. It entails the presence of organ failure, the time elapsed < 24 h before surgery, presence of malignancy, origin of sepsis, faecal peritonitis and generalised peritonitis [43]. The Mannheim peritonitis index score may assist surgeons in identifying and aggressively managing high risk patients so as to improve outcome [9].

Patient factor

Patient factors include (1) Advanced age (>70 years) but it is important to distinguish chronological age from physiological age, (2) Comorbidity (Chronic renal failure, COAD, liver failure, obesity), (3) Malnutrition (> 20% weight loss), (4) Pre-existing remote body site infection, (5) Immune organ response (host-defence mechanisms), (6) Disease process/shock, (7) Immune suppression (Diabetes mellitus, HIV/AIDS, Steroids), (8) Perioperative hyperglycaemia (Insulin resistance), (9) Lifestyle (smoking, alcohol abuse). The most important prognostic factor in emergency colorectal surgery is age and faecal peritonitis. Together the mortality is > 60% as the toxemia and rapid severe Systemic Inflammatory Response Syndrome (SIRS) in faecal peritonitis overwhelms the aged [21,25].

Advanced age: Many older patients underwent relatively more complex and contaminated operations, and a greater proportion of elderly patients had major emergency procedures [44]. Phillips et al. [45] demonstrated a 1 in 3 chance (33%) of in hospital mortality following emergency surgery in > 80 year olds with malignant large bowel obstruction. In elective surgery, <80 year olds had 8% in-hospital mortality and 16% mortality for radical rectal cancer surgery in > 80 year olds. Widdison et al. in 2011 [46] reported an improved 30 day mortality (4% elective surgery; 14% emergency surgery), mostly elderly from medical complications and comorbidities. There was an improved 16% postoperative mortality after emergency surgery in > 80 year olds and a 1% postoperative mortality in the < 59 year olds, presumably due to improved perioperative care. The post-operative mortality increased by 3% every 10 years after elective resection but increased by 8% every 10 years after emergency resection. The probability of dying from colorectal cancer (CRC) declined with age (50yrs- 1/2 died, 70yrs- 1/3 died, 80yrs- 1/4 died). Given the increased post-operative mortality in the elderly and reduced likelihood of them dying from colorectal cancer, the question is should all elderly patients undergo a radical resection. There should therefore be selection of those most to gain from radical operation, improved preoperative assessment and optimisation and the improved provision of HDU/ICU beds may reduce postoperative morbidity and mortality.

Lifestyle (Smoking and alcohol abuse): Following multiple regression analysis where well known risk factors for anastomotic leakage such as site of anastomosis, age and stage of training of the surgeon were taken into account, Sorensen et al. [47] showed that smoking and alcohol abuse are important predictive factors for anastomotic leakage after colonic and rectal resection. Due to the effect on the microcirculation smokers, compared with non-smokers, had an increased risk of anastomotic leakage (Relative Risk (RR) 3.18 (95% c.i. 1.44-7.00) as with alcohol abusers compared with abstainers (RR 7.18 (95% c.i. 1.20-43.01).

Host- defence mechanisms: It is not possible to practice fully the ideal management of early diagnosis and surgery for the acute abdomen, thus reducing morbidity and mortality to zero because the patients and the disease are variable [1,48]. A pain-free abdomen may occur in older people, children, immunocompromised, last trimester of pregnancy and the sedated and paralysed ICU patient [48,49]. Why is it that a patient with minimal bacterial contamination at surgery may develop a pelvic abscess, whereas another patient with faecal contamination after a stercoral perforation of the colon may

Table 1: Cytokines.

Pro-inflammatory	Anti-inflammatory	Acute phase reactants
Tumour necrosis factor (TNF α)	Interleukin-10 (IL-10)	Achymotrypsin
Interleukin-1 (IL-1)	Prostaglandin E ₂ (PGE ₂)	Complement C3
Interleukin-2 (IL-2)	Transforming growth factor (TGF β)	Caeruloplasmin
Interleukin-6 (IL-6)	Interleukin-4 (IL-4)	Fibrinogen
Interleukin-8 (IL-8)		Haptoglobin
Interferon (IFN γ)		C-reactive protein (CRP)

not develop infective complications? The answer would be derived from a better understanding about susceptibility to endogenous infection [1]. All surgical wounds will be contaminated with bacteria during surgery but only a small percentage becomes infected. The patient's host defences are capable of controlling and eliminating the offending organisms if the inoculums are small and the contaminant not overwhelming [50]. The risk of surgical site infection is inversely proportional to the resistance of patient to infection as illustrated in the Patient-related surgical site risk equation: *Risk of SSI = Dose of Bacteria contaminant x Virulence of microorganism/ Resistance of patient to infection* [2]. There is a balance between excessive and inadequate responses to infection. An excessive or prolonged activation of the cellular/humoral mediator pathway would lead to an evolution of a cytokine cascade (TNF, IL-1, IL-6, IL-8) and a sustained activation of the reticuloendothelial system (SIRS) leading to secondary inflammatory mediators causing multiple organ failure (MOF) and death [51]. Sepsis is an evolving process and mortality increases with the degree of SIRS. The mortality of bacteraemia (5%), Sepsis (*infection + SIRS*) (15%), Septic shock (*systolic BP < 90mmHg*) (50%), Severe SIRS (80%), MOF (90%) [51,52]. In severe SIRS the cytokine cascade is fully in progress and surgical intervention is late and usually of no avail. Gut mucosal hypoperfusion as an early consequence of hypovolaemia may continue to drive the inflammatory process even when the initial causal factors are dealt with. Supportive treatment may be all that is required as there is as yet no known drug to abort this cascade [53]. Several multicentre randomized trials using monoclonal antibodies or antagonists to endotoxin, TNF and IL-1 as adjuvant to the established basic principles of management have not reduced mortality and it is now recognized that the redundancy in the inflammatory response is such that if one component is removed, another mediator will continue the response. Moreover, if the pool of endogenous antagonists (e.g. IL-1 receptor antagonist or soluble TNF receptors) is replete, addition of exogenous antagonists is unlikely to be efficacious [51,53,54]. Once one organ system has failed, others typically follow (organ failure amplification) and when three or more systems have failed the ensuing mortality approaches 80 - 100% and [54]. Thus, it is important to strive to support as far as possible each organ system to avoid each further adverse event (e.g. ventilation, haemofiltration/haemodialysis, inotropic support, use of blood products) [22].

Immune response and Surgical/ Metabolic stress: Immune response and metabolic regulation are highly integrated as their pathways have been evolutionary conserved throughout species. The proper function of each is dependent on the other [5,55]. The complex network of cytokines balances pro-inflammatory and anti-inflammatory effects and an imbalance or the uncontrolled

production of cytokines can result in inflammatory disease [55,56] (Table 1). Cytokines are helpful during the host response but potentially hazardous if uncontrollable or in excess. Thus, minor operations may stimulate the immune response but the effect of major surgery is immunodepression [57,58]. After major surgery pro-inflammatory cytokine secretion by T lymphocytes are suppressed causing increased susceptibility to the intracellular pathogens such as *Listeria* and *mycobacteria* [59]. The anti-inflammatory cytokines (PGE₂, TGF β) decrease monocyte function. TGF β decrease IL-17 that provides anti-microbial immunity at epithelial/ mucosal barriers against a *candida* and *staphylococcus* [60]. IL-10 down regulates MHC II of monocytes which correlates with clinical outcome and the development of infection following surgery due to defect in neutrophil chemotaxis, phagocytosis and lysosomal enzyme contents. Thus, it seemed reasonable to attempt to adjust this MHC Class II antigen level by administering interferon (IFN γ). This may benefit those whose post-traumatic MHC class II recovery was delayed or did not recover at all [61]. However, the multiplicity of factors that influence the outcome of major surgery and the variability of the individual's response especially with their initial level of receptor expression will confound the effect [1,5]. Although the increased anti-inflammatory cytokine ((IL-10) secretion by monocytes after major surgery may be a homeostatic response it would be interesting to know how much of these may be the effect of the post- operative hyperglycaemia ('diabetes of injury') as a result of the insulin resistance from surgical stress/ injury.

Post- operative hyperglycaemia (Insulin resistance): The post- operative hyperglycaemia after major colorectal surgery is due to insulin resistance as a result of the antagonistic affects of the surgical stress (catabolic) hormones especially catecholamines and the complex immunophysiological response to the uncontrollable or excess cytokines. The organs affected are those with no insulin receptors nor storage capacity such as the kidney, endothelial of blood vessels and heart, blood cells and neural tissue, and thus an uncontrolled inflow of glucose causing early and late complications including surgical site infections [62,63]. It responds rapidly to insulin treatment as compared to a traumatic patients with type-2 diabetes. The Enhanced Recovery after Surgery (ERAS) is a multimodal approach developed by surgeons in Europe aimed at reducing metabolic stress after surgery and thus decreasing insulin resistance and post- operative hyperglycaemia [64]. By using one facet of this protocol, the pre-operative anabolic setting of the patient with a carbohydrate (CHO) drink, perioperative care was optimised through the prevention of post- operative hyperglycaemia, decrease post-operative infection, SSI and length of hospital stay [65]. This is corroborated by the fact that the anti-inflammatory cytokine

(IL-10) secretion by monocytes decrease during preoperative CHO loading but increase in fasting [57,58]. Because many operations are accompanied by haemorrhage the post-operative immune depression may also be caused in part by blood loss and cellular hypoxia rather than surgery [66,67]. Perioperative blood transfusion may also contribute to immunosuppression but the underlying mechanism is largely unknown [68].

Immune deficiency (HIV/AIDS): The Human Immunodeficiency Virus (HIV) is an RNA retrovirus that infects human T lymphocytes, transmitted by contaminated body fluids and after a variable period of up to 2 years it produces diminished immunological function which is manifest as the Acquired Immune Deficiency Syndrome (AIDS). It is a major epidemic of the century but these patients are heterogenous. Patients with CD4 T- lymphocyte count > 500cells/ul have mild disease and of same risk as non-HIV patients. Patients with 200-499 CD4 have advanced disease and require ICU if major surgery is required. Patients with < 200CD4 have AIDS and only life-saving surgery may be rendered [69,70]. Highly Active Antiretroviral Therapy (HAART) improves resistance to infection and nutrition and provides better surgical outcome [71]. The factors increasing operative morbidity and mortality are poor ASA, physiologically demanding surgery, emergency surgery and operations in contaminated field e.g. anorectum, oral cavity. AIDS patients with more advanced disease, low CD4 counts (<100) or poor performance status are at increased risk for poor wound healing following haemorrhoidectomy, and the benefits of resolution of symptoms must be balanced against this risk [72,73].

In summary, sepsis source control failure in colorectal surgery are more likely in patients with delayed (>24 hours) procedural intervention (*Patient/ surgeon factor*), higher severity of illness- (APACHE >15 (*patient/disease factor*), advanced age- >70yrs (*patient factor*), co-morbidity (*patient factor*), poor nutritional status (*patient factor*) and a higher degree of peritoneal involvement - a high MPI score (*disease factor*). This would be heralded by persistent or recurrent intra-abdominal infection, anastomotic failure or fistula formation.

Conclusion

The most important prognostic factors in emergency colorectal surgery are the preoperative status - age and faecal peritonitis. Thus, peritoneal sepsis is seldom the sole cause of death, but compounds coincidental cardiovascular, respiratory or renal pathology. Inter-individual variation in the pattern of mediator release and of end organ responsiveness determines the initial physiological response to major sepsis and may be the key determinant of outcome. Perioperative care strives to support as far as possible each organ system to avoid organ failure amplification. The prevention of gut mucosal acidosis in the critically ill patient on ICU may also improve outcome. The empiric choice of the surgical technique/ procedure is predominantly determined by the patient status and the disease. The patient factor thus has a greater impact than the surgeon-factor on the prognosis of sepsis in emergency colorectal surgery. In both elective and emergency colorectal surgery, the surgeon factor remains the single most important factor that can influence the morbidity and mortality from sepsis.

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