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REVIEW

Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: a systematic review

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Abstract
Purpose Surgical management of inflammatory bowel disease (IBD) is a challenging task. The aim of preoperative optimization (PO) is to decrease the risk of complications and reduce the length of postoperative stay. The aim of this study was to review and grade the available evidence, attain clear recommendations, and point out potential future research.
Methods Studies were identified from electronic databases (PubMed, Embase, and Cochrane Library) and scanning reference lists in relevant papers. English-written studies examining PO in adult patients with IBD were included. Eight PO factors were investigated.
Results Management of IBD is a multidisciplinary task. Steroid withdrawal is recommended while steroid stress dose is not recommended. Thiopurines appear to be safe, but it may be prudent to plan the procedure remotely from the last dose of an anti-TNF agent. Nutritional risk screening is recommended to unveil and correct any malnutrition. Thrombosis prophylaxis prior to surgery is well supported by evidence while extended 4-week prophylaxis needs further research. Percutaneous ultrasound or CT-guided drainage for intra-abdominal abscesses is recommended, but it is unclear for how long supplementary antibiotics (ABs) should be used. Oral AB 24 h prior to open surgery might improve outcome if given as complementary to IV perioperative AB. Mechanical bowel preparation is not supported by evidence. Comorbidities must be treated accordingly prior to surgical intervention. Smoking cessation can be beneficial for wound healing.
Conclusion Multimodel PO intervention in IBD patients is recommended.

Keywords Inflammatory bowel disease · Optimization · Surgery · Multimodel intervention · Colorectal

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Introduction

Surgical management of inflammatory bowel disease (IBD) still presents a challenge for surgeons. The timing of operation depends on disease severity, disease presentation, medical treatment, patients' perspectives, and preoperative optimization (PO) [1]. PO is used to bring the patient in optimal condition to surgery and to reduce the risk of unfavorable postoperative outcome [2]. PO in patients with IBD is often suboptimal, and the evidence supporting it is scanty. Therefore, the subject calls for more attention [3]. PO includes different categories of support; for example, optimization of medical treatment has been studied and demonstrated that steroids have a negative effect on postoperative outcome [4, 5]. The effect of immunomodulators and anti-tumor necrosis factor (TNF)-alpha treatment is more controversial [6]. Another factor is age. The proportion of older patients among those with IBD is increasing, resulting in an increased population of patients with comorbidities that requires preoperative attention

[7]. Nutritional support has also been shown to be a key factor for surgical candidates with IBD [8, 9]. The same applies for thromboembolism prophylaxis. Patients with IBD have a three-fold increased risk of developing deep venous thrombosis (DVT) or pulmonary embolism (PE) [10, 11]. However, the best anti-thrombosis regime has not been thoroughly investigated for this particular group of patients. Few studies have investigated the use of preoperative antibiotics [12]. Smoking is a well-known risk factor for postoperative complications especially in patients with Crohn's disease (CD) [13, 14]. Yet, optimization with a smoking-free period prior to surgical intervention has not been studied. Many studies suggest that percutaneous abscess drainage (PAD) is safe, effective, and reduce the postoperative complication rate in patients with CD [15–17]. A multimodel intervention using a combination of all the factors mentioned might play a role in improving the postoperative outcome for operated patients with IBD. Only a few reviews addressed the issue of PO in patients with IBD [7, 18–20]. Guidelines exist for some of the elements of PO, but specific guidelines for IBD patients are lacking [21, 22]. The aim of this review is to provide evidence-based clear recommendations about PO of patients with IBD and point out possible interventions for future research.

Materials and methods

A predefined PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) protocol was developed and implemented throughout the review [23]. The PRISMA figure was modified to accommodate eight different elements in one figure instead of drawing eight different PRISMA figures.

Inclusion and exclusion criteria

Studies were included based on assessment of the following preoperative optimization factors in adult patients with IBD: pharmacological considerations (preoperative medical treatment and steroid stress dose), nutrition, thrombosis prophylaxis, treatment of preoperative sepsis, prophylactic antibiotics (AB), bowel preparation, smoking cessation, and treatment of comorbidity. The included studies were original studies, reviews, and guidelines published between 2005 and July 2015 to ensure up to evidence.

Articles in languages other than English were excluded. Case reports, letters to editors and conference abstracts were excluded. Studies investigating optimization factors not related to the preoperative preparation were also excluded.

Outcome measures

The primary outcome measure investigated in the studies included was postoperative complications. Secondary outcome measures were length of postoperative stay (LOS), readmission rate, and mortality.

Search strategy

Studies were identified from electronic databases, references from relevant papers, and correspondence with experts in the field. The search was conducted in MEDLINE, Embase, and the Cochrane Library. The last search was conducted on July 31, 2015.

Optimization factors were divided between the authors, and each author conducted their own systematic search, which was repeated by a research specialist in order to ensure that all eligible studies were included. The search file for MEDLINE is attached as Appendix. The same keywords were applied for searching Embase and Cochrane Library.

All studies identified were screened for inclusion—primarily based on abstract and then by full-text screening. All authors performed the screening of studies and decided whether these met the inclusion criteria. A modified PRISMA flowchart of the included/excluded studies is shown in Fig. 1.

Assessment of bias

The heterogeneous nature of the included studies did not allow assessment of bias. Some of the included reviews have actually assessed bias, and these are pointed out in the text when applicable.

Grading of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24] was used to describe the level of evidence of the included studies. Table 1 shows GRADE.

Pharmacological considerations prior to IBD surgery

1. Preoperative medications

There is an abundance of data regarding the impact of anti-inflammatory treatments on subsequent surgery. Unfortunately, all the available studies were retrospective and varied significantly in methodology. In this systematic review, we identified 14 eligible studies regarding the effect of preoperative medications on the postoperative outcome in patients with IBD [5, 14, 25–36].

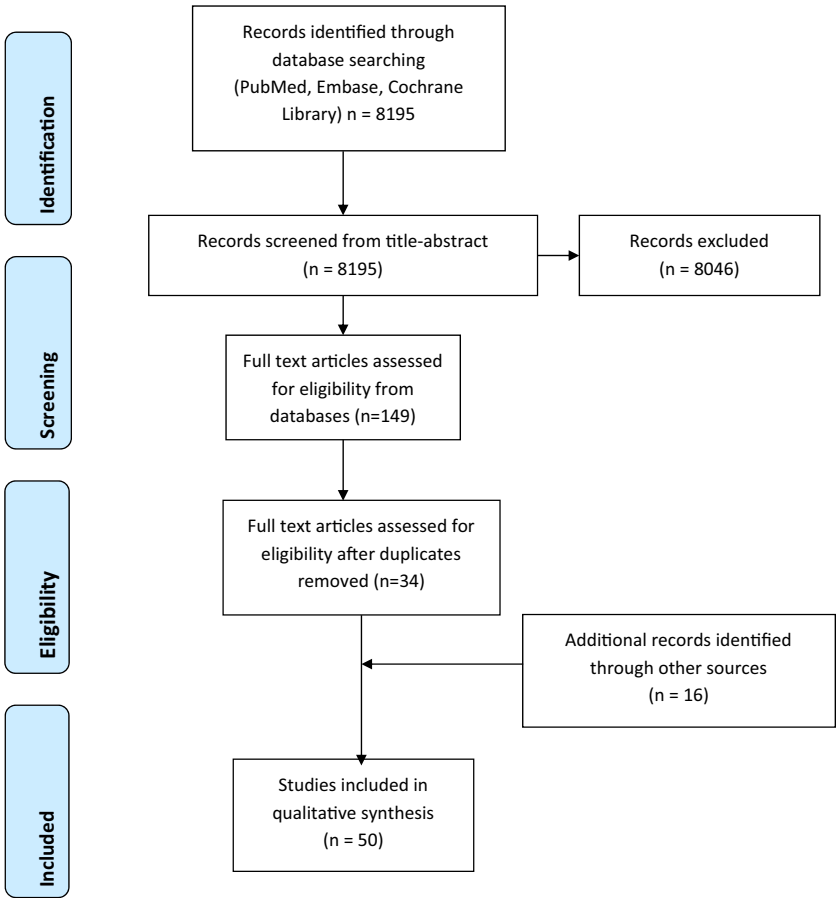

Fig. 1 Modified PRISMA flowchart

The majority of data refers to the impact of corticosteroids on surgical outcome. A meta-analysis of observational studies in IBD patients found an increased risk of all postoperative complications (OR 1.41; 95% CI 1.07–1.87), as well as an increased risk of postoperative infectious complications (OR 1.68; 95% CI 1.24–2.28) among patients on steroids [5]. This risk was dose-related. Newer studies support these results [27]. The unfavorable effects of corticosteroids is most likely mediated by both an increased susceptibility to infections, as well as by the negative impact that corticosteroids carry with wound healing [5].

Table 1 The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach used to describe the level of evidence in the included studies

Evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies and case–control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Recommendation strength	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

Immunomodulators effect on postoperative complications is less studied. A review by Subramanian summarized data from 11 small retrospective studies [32]. None of the studies found increased risk of postoperative complications associated with using thiopurines or cyclosporines. This finding is supported by a recent review [25] and only challenged by one study that reported an increased risk of postsurgical intra-abdominal septic complications in CD patients receiving azathioprine preoperatively (OR 3.7; 95% CI 1.0–13.1; $P = 0.04$) [29]. Importantly, this study is probably the largest to date and included a more homogenous population that consisted of CD patients only. However, it should be noticed that the clinical effect of thiopurines gains and loss effect slowly (within up to 3 months). Therefore, it is unlikely that stopping thiopurines before surgery will have any measurable impact on risk of complications [37]. Moreover, there is no evidence to suggest that patients with acute severe colitis that received treatment with cyclosporine have a higher rate of complications [30, 32].

Multiple studies addressed the risk of postoperative complications in patients with IBD, exposed to anti-tumor necrosis factor-alpha (anti-TNF-α) agents. The largest single-center studies to date were published by Waterman [34], Syed [33], and Morar [14]. Waterman et al. specifically examined rates of postoperative infectious complications in relation to the duration between exposure and surgery in a cohort of 195 patients with IBD who underwent 473 surgical procedures. No increased rate of postoperative infectious complications, anastomotic complications, or overall complications was noted in comparison to matched controls [34]. The study investigated the effect of exposure to biologics within 180 days of abdominal surgery. The low drug concentration over such long period and the presence of anti-drug antibodies might have rendered the drug ineffective (unpublished work by the authors). Syed et al. described 211 patients with CD who underwent 325 surgical procedures and showed that preoperative anti-TNF-α was an independent predictor of overall infectious (OR 2.43; 95% CI 1.18–5.03) and surgical site infections (OR 1.96; 95% CI 1.02–3.77). Morar et al. examined risk factors for intra-abdominal septic complications (IASCs) in a CD cohort with 163 patients undergoing resection and found biological therapy to be an independent risk factor in a multivariate analysis (OR 24.6; 96% CI 2.0–298.1; $P = 0.01$) [14].

Several meta-analyses attempted to summarize the data about the effect of anti-TNF-α on postoperative outcome using the available studies [26]. Most of these publications suffered from the inherent limitations of meta-analyses devoted to retrospective studies, such as reporting and recruitment bias, variable quality of the included studies, missing data, variability in definitions of patient cohorts, types of complications, duration of exposure, time from last dose to surgery, and effect of concomitant treatment. A meta-analysis by Yang et al. showed no significant association between infliximab (IFX) therapy and total infectious and non-infectious postoperative complications in patients with ulcerative colitis (UC) [35]. However, this was not the case in patients who underwent restorative proctocolectomy with primary ileal pouch formation [31]. Selvaggi et al. analyzed seven papers, including 162 patients receiving biologics and 468 controls, all undergoing primary pouch formation. Patients receiving IFX were more likely to develop both early (OR 4.12; 95% CI 2.37–7.15; $P = 0.001$) and postileostomy closure (OR 2.27; 95% CI 1.27–4.05; $P = 0.005$) anastomosis-related complications. Numbers needed to harm were five and four, respectively. They found that administration of three or more IFX effusions increased the risk of early complications. However, the rate of complications was not increased if IFX was administered within 12 weeks before surgery, when compared with a longer delay. Several meta-analyses assessed the risk of postoperative complications in CD patients receiving anti-TNF-α agent. These meta-analyses attained converging results due to methodological differences [26, 36]. However, an increased risk of postoperative complications was seen in most of these meta-analyses.

The question whether drug concentration plays a role in postoperative outcome was addressed in two studies. In the study by Waterman et al., 19 patients had available measurements of trough levels; patients with detectable preoperative infliximab levels had similar rates of wound infection compared with those with undetectable levels [34]. A larger study included 150 patients with IBD and available anti-TNF preoperative trough-level measurements [28]. In the UC group, there was no difference between patients with and without detectable trough levels. However, in the CD group, postoperative morbidity (OR 2.5; 95% CI 1.07–5.85; $P = 0.03$) and infectious complications (OR 3.0; 95% CI 1.08–8.43; $P = 0.03$) increased in patients with trough levels ≥ 3 μg/mL [32]. Also, overall postoperative morbidity ($P = 0.047$) and readmissions ($P = 0.043$) were more frequent with levels ≥ 8 μg/mL, compared with levels ≥ 3 μg/mL, indicating that higher levels increase complication risks.

Importantly, the vast majority of studies about anti-TNF-α included patients treated with IFX. To the best of our knowledge, no data addressing newer anti-TNF-α such as certolizumab and golimumab are available. Similarly, there are no reports on postoperative risk with non-anti-TNF biologics such as vedolizumab and ustekinumab.

Evidence level IIb regarding preoperative steroids, III regarding thiopurines and anti-TNF-α.

Recommendations Steroid withdrawal is highly recommended in preoperative period. Thiopurines appear to be safe. For elective surgeries, it is recommended to plan the procedure few weeks from the last dose of an anti-TNF agent, although the recommended duration of such delay is unclear.

Potential for future researches Well-designed prospective studies investigating the impact of steroids, immunomodulators, anti-TNF-α, and non-anti-TNF biologics (such as vedolizumab and ustekinumab) on postoperative outcomes are warranted.

2. Steroid stress dose

Supplementary supraphysiological dose of perioperative glucocorticosteroid or "corticosteroid stress scheme" has been recommended in patients receiving steroids prior to surgery [38]. The assumption that patients receiving steroids have a depressed adrenal function, and therefore cannot produce sufficient steroids in case of stress situation is poorly supported by scientific evidence [39–41]. There is a widespread disagreement about the amount, duration, and total exposure of exogenous steroids required to cause HPA axis dysfunction, and the duration the glands take to fully regain function after discontinuation of therapy [40].

Four reviews evaluating five prospective studies, seven retrospective studies, one experimental study, and two RCTs showed no evidence to support the use of preoperative stress dose [39–43]. However, patients on high-dose steroids who could not be weaned of steroids can receive low-dose preoperative steroids [44]. The ESCP-ECCO consensus statement admitted that there is no evidence to support this practice and called for challenging it, but it did not change the current recommendation yet [37].

Evidence level Ib.

Recommendations Gradual withdraw of steroids should be attempted, so that the patient is steroid free for 1 week prior to surgery. If this is not possible, the patient should continue to use daily steroid dose preoperatively with no need for extra steroids. These recommendations do not apply to patients who receive physiologic replacement doses of corticosteroids due to primary dysfunction of the hypothalamus-pituitary-adrenal axis (e.g. patients with primary adrenal failure due to Addison disease).

Potential for researches Larger RCTs are needed to define the risk of postoperative adrenal insufficiency and to establish standardized practices for perioperative steroid therapy.

Nutrition

An abundance of studies describe the effect of nutritional therapy on remission of IBD, but the evidence of nutrition as a PO factor is less studied [45, 46]. There are two rationales for nutritional support prior to surgery. First, treatment of malnutrition is advised since it has been well established that malnutrition is an important risk factor for postoperative complications and mortality [47]. The second is to modify the underlying inflammatory process and reduce disease activity prior to surgery.

Three retrospective studies investigated parenteral nutrition (PN) as a PO factor for IBD [8, 48, 49]. Jacobsen compared 15 patients with CD who were given preoperative total parenteral nutrition (TPN) with matching controls operated without preoperative TPN and showed a significant higher rate of postoperative complications in the control group (n = 29/105 vs. 0/15; $P < 0.05$) [8]. Yao et al. compared severely malnourished patients with CD who were given preoperative PN with patients without preoperative PN [49]. The study showed no difference in complication rate between the two groups (control group 26.5%; study group 27.3%; $P = 0.86$). Salinas et al. compared the postoperative complication rate of 56 patients with UC who received preoperative TPN with 179 who did not [48]. The study showed that the TPN group had higher complication rate (OR 2.32; $P = 0.04$). However, when line infections where excluded, there were no significant difference in complication rate.

A small retrospective study looked at preoperative management in 78 patients with penetrating CD [12]. Univariate analysis showed no association between preoperative EN and/or PN and occurrence of postoperative complications.

Two studies evaluated exclusive enteral nutrition (EEN) as a PO factor for patients with CD [50, 51]. Li et al. investigated EEN in patients receiving immunosuppressive therapy with preoperative drug-free interval [51]. In multivariate analysis, EEN demonstrated to be a risk-reducing factor for both infectious (OR 0.53; 95% CI 0.32–0.86; $P = 0.011$) and non-infectious postoperative complications (OR 0.35; 95% CI 0.18–0.67; $P = 0.001$). They found no significant difference in readmission rates related to EEN therapy. Li et al. investigated the influence of preoperative 3-month EEN on the postoperative incidence of IASCs [50] including anastomotic leakage, intra-abdominal abscesses, and enteric fistulas. At 3-month follow-up, the EEN group demonstrated a lower risk for IASCs (3.6 vs. 17.6%; $P = 0.020$) when compared to the control group, but at 2-year follow-up, the two groups had comparable risks.

Wagner et al. reviewed nutritional support of surgical patients with IBD and concluded that malnutrition, as well as preoperative goals for nutritional supplementation, needs further definition [9]. The review did not investigate the relation between preoperative malnutrition and poor postoperative outcome. Three reviews evaluating different factors of PO for CD assessed the question of nutritional therapy [18–20]. They all conclude that nutritional support for malnourished CD patients prior to surgery is important and that TPN should only be used for those who cannot tolerate EN. Spinelli et al. suggested that nutritional support is warranted for 10–14 days prior to surgery and preferably enteral [20].

The ability to optimize the nutritional status is of great importance, and all IBD patients should be screened for malnutrition preoperatively. There is no standardized test for malnutrition. However, ESPEN (The European Society for Parenteral and Enteral Nutrition) guidelines for nutrition screening recommend NRS-2002, which primarily considers four clinical parameters: BMI, weight loss, reduced dietary intake, and severe illness [52]. Zhu et al. investigated the best endpoint of successful preoperative nutritional intervention in a randomized clinical trial and found that reduction of inflammation is a sufficient endpoint in patients with CD waiting for surgery. It took 25.57 ± 11.68 days in average to achieve a significant reduction in inflammation [51].

Evidence level III.

Recommendations Screening for malnutrition with NRS-2002 or a similar screening tool is recommended to guide a nutritional care plan. The duration of nutritional support prior to surgery depends on the individual patients' response to dietary changes. The type of nutrition therapy (e.g., TPN vs. EN) could not be decided based on available studies, since they are contradictory and heterogeneous.

Potential for future research Large prospective studies comparing different types and duration of preoperative nutrition are needed. Most of the published literatures describe CD, and therefore, more studies investigating UC are needed.

Thrombosis prophylaxis

It is well established that patients with IBD carry a high risk of venous thromboembolism (VTE) [53–55]. The mechanism of hypercoagulability in IBD is multifactorial and consists of acquired factors such as inflammation, vitamin deficiencies, surgery, steroid therapy, and fluid depletion along with a prothrombotic condition and hypercoagulability state [54]. Papa et al. recently reviewed the guidelines and data about prevention and treatment of VTE in patients with IBD [56]. All current guidelines recommend the use of anticoagulants to prevent VTE in all hospitalized IBD patients. Recommended anticoagulants are low molecular weight heparin, unfractionated heparin, or fondaparinux. Less data is available specifically for thrombosis prophylaxis in patients with IBD undergoing surgery.

In our systematic review, we identified six retrospective studies investigating the incidence of postoperative VTE in patients with IBD [11, 57–61]. Gross et al. compared VTE rates in 8888 IBD cases compared with 37,076 colorectal cancer who underwent surgery [57]. After controlling for covariates, the OR for VTE was 1.26 (95% CI 1.02–1.56; $P = 0.03$) for IBD patients when compared with patients suffering from colorectal cancer. Extensive thrombosis prophylaxis for 4 weeks following surgery is recommended for patients with colorectal cancer [62]. Because the incidence in IBD was found to be higher than the cancer group, the authors suggested an extension of the postoperative thrombosis prophylaxis after IBD-related surgeries. It is important to note that the study has a large bias in terms of missing information about thrombosis prophylaxis given to the cancer group. The same bias is a problem in the study of Merrill and Millham who compared 2249 patients with IBD with 269,119 surgical patients without IBD [59]. They found IBD patients to have a significantly increased risk of DVT and PE (OR 2.03; 95% CI 1.52–2.70; $P < 0.001$) following surgery. No data was available on the thrombosis prophylaxis given to the two groups.

Another retrospective study with methodological flaws assessed DVT and PE in patients with UC [60]. No multivariate analysis was done; however, the authors calculated the thrombosis incidence on an intention to treat analysis to be 1.7%. They found this acceptable and concluded that there is no need for extended thrombosis prophylaxis following surgery for UC. Kaplan et al. found an increased risk of VTE among surgical patients with UC compared with medically treated patients [58]. The risk of VTE after emergency colectomy was 8.7 and 4.9% after elective colectomy despite the fact that > 90% of the patients received postoperative heparin prophylaxis. However, only < 20% of the patients who underwent emergency colectomy were given preoperative heparin. Although the length of postoperative heparin treatment following surgery was not indicated, these results suggest the need for preoperative as well as postoperative thrombosis prophylaxis.

Scarpa et al. aimed to evaluate the efficiency of prophylactic low molecular weight heparin therapy with DVT prevention in IBD patients undergoing surgery compared with other colorectal operate patients [11]. All patients received daily 4000 IU postoperative low molecular weight heparin, for the duration of their hospital stay, and graduated compression stockings for the duration of the surgical procedure. After adjusting for confounders, only UC trended to be a predictor of DVT in a multiple logistic regression analysis (OR 5.9; 95% CI 0.9–39.7; $P = 0.065$). This finding was confirmed by another study [61] where VTE occurred more frequently in UC patients compared to CD patients (3.3 vs. 1.4%; $P < 0.001$).

Altogether, there are no prospective studies concerning thrombosis prophylaxis prior to IBD-related surgery. Most retrospective studies published are of poor quality with problematic methodology. It seems that patients with IBD, especially UC, undergoing surgery has a higher risk of VTE compared with other surgical patients.

Evidence level III for preoperative thrombosis prophylaxis and IV for extended postoperative thrombosis prophylaxis.

Recommendations Patients with IBD, who are not at high risk of bleeding, should receive pre- and postoperative anticoagulants during their hospital stay in order to prevent VTE. The evidence supporting 4-week thrombosis prophylaxis after discharge is scanty.

Potential for future research Prospective studies comparing different regimes and duration of pre- and postoperative anticoagulant treatment.

Treatment of preoperative sepsis

The presence of intra-abdominal abscess at the time of surgery is a known independent risk factor for postoperative septic complications [14, 47]. Treatments include ABs, percutaneous abscess drainage (PAD), and surgical drainage (SD). There is a significant increase in the use of PAD and a reduction in SD. Presence of complicated disease significantly increases the likelihood of undergoing SD [15].

Two retrospective studies and two reviews described the influence of preoperative PAD on postoperative complications in patients with CD [16, 18, 20, 63]. A retrospective study of 25 patients with CD compared the incidence of severe IASCs in patients undergoing intestinal resections with and without PAD prior to definitive surgery [16]. PAD was performed in 12 patients with an average of 37 days (6–83) prior to surgery and significantly reduced the occurrence of severe postoperative IASC (PAD group 25% vs. non-PAD group 69%; $P = 0.04$). In addition, the LOS was shorter in the PAD group (mean 11 vs. 19 days; $P = 0.04$). In contrast, Bafford et al. in a retrospective cohort of 70 CD patients found no difference in septic complications between patients treated with PAD in addition to surgery compared with surgery alone ("PAD + surgery" group 20.0% vs. "surgery alone" group 31.3%; $P = 0.40$) [63]. A review by Efron et al. concluded that PAD should be performed preoperatively in all accessible cases for a better postoperative outcome [18]. Spinelli et al. came to the same conclusion, although the authors recommended adding AB therapy [20].

In conclusion, the retrospective studies show divergent evidence about the effect of PAD on the risk of postoperative complications in CD, but reviews evaluating research published prior to 2005 show clear preference for PAD when possible.

Evidence level III.

Recommendations Ultra-sound or CT-guided drainage of abscess is recommended prior to surgery, preferably with antibacterial coverage. There is no clear recommendation in the literature about how many days/weeks after abscess drainage surgical intervention should be performed.

Potential for future research There is need for studies investigating PAD with and without AB, as well as further research on the appropriate interval between abscess drainage and surgical intervention.

Prophylactic antibiotics

Administration of AB prophylaxis prior to surgery is nowadays embedded into surgical practice with significant effect on the rate of surgical site infections (SSIs) [64]. Timing of administration is widely discussed in many surgical practices, but the evidence is lacking in IBD [64]. In this review, we included one RCT, two retrospective cohort studies, and one review assessing the use of prophylactic antibiotics in patients with IBD undergoing surgery.

A RCT on patients with UC tested the effect of preoperative oral AB 24 h prior to surgery plus IV perioperative AB compared with IV perioperative AB alone [65]. The study concluded that the preoperative oral AB reduced the number of incisional SSI (4.1 vs. 22.4%; $P = 0.001$) but had no effect on organ and space SSI (2.1 vs. 2.0%; $P = 0.872$). The study examined only open approach restorative proctocolectomy procedures. Laparoscopic approach has been shown to reduce postoperative morbidity [66]. A Cochrane review by Nelson et al. demonstrated high quality evidence that AB, covering aerobic and anaerobic bacteria delivered oral and/or intravenous prior to elective colorectal surgery reduce the risk of surgical wound infection by as much as 75% [30]. Morris et al. retrospectively reviewed over 8000 patients who underwent colorectal surgery, of which 551 were operated for IBD and concluded that perioperative AB decrease SSI (OR 0.44; 95% CI 0.36–0.53; $P < 0.001$) and reduce LOS (OR 0.90; 95% CI 0.87–0.94; $P < 0.001$) and readmission rate (OR 0.74; 95% CI 0.61–0.91; $P = 0.01$) [67]. The study examined the efficacy of oral AB along with mechanical bowel preparation and was limited due to unspecified antimicrobial therapeutic methodology. Both Nelson and Morris included IBD patients among others and performed no subgroup analysis.

The effect of AB therapy for a longer period other than the routine perioperative administration is still unclear. Only a handful of studies have investigated the subject, without randomization or control groups. Zerbib et al. described 78 patients with CD who underwent PO including over 2 weeks of intravenous AB, withdrawal from steroids and immunosuppressive therapy, abscess drainage, and nutritional support [12]. The study showed low rates of morbidity (18%) and no mortality in treated patients. However, the series was not controlled and suffered from high risk of selection bias.

Evidence level Ib for UC (for oral AB 24 h prior to surgery) and III (for longer preoperative AB treatment).

Recommendations Oral AB 24 h prior to open surgery should be given complementary to IV perioperative AB. Longer perioperative AB treatment is not supported by evidence.

Potentials for future researches Duration of AB prior to surgery, type of AB regime, and route of administration needs to be investigated in both CD and UC patients in prospective studies.

Bowel preparation

Although bowel preparation prior to surgery is discussed extensively in the literature, there is little data about this preoperative measure specifically in patients with IBD. Literature on the subject refers to IBD as part of a larger group of diseases treated surgically. Spinelli et al. compared a group of 20 patients with CD with enhanced recovery pathway (ERP) protocol without mechanical bowel preparation to a historically matched cohort of 70 patients [68]. The study showed significantly earlier return of bowel function and shorter length of stay in the ERP group. A more recent study by Morris et al. reviewed over 8000 patients from the National Surgical Quality Improvement Program (NSQIP) database, comparing patients that received mechanical bowel preparation with or without oral antibiotics with patients who did not receive bowel preparation [67]. The authors concluded that mechanical bowel preparation along with oral antibiotics prior to surgery could reduce the rate of SSIs, LOS, and readmission rate. However, although the authors mention IBD patients as a subgroup in their analysis (6.6% of patients included in the database), there is no reference in the data whether there is an advantage in this group specifically. The subject of bowel preparation is under extensive research in the last two decades with several RCTs and subsequently systemic reviews and meta-analysis indicating that there is no benefit to mechanical bowel preparation prior to elective colorectal surgery [69–71]. However, recent large-scale studies like the Morrison et al. study mentioned above, though not randomized or controlled, suggest that mechanical bowel preparation along with oral antibiotics can contribute to a better surgical outcome. This conclusion is supported by a recent database study that showed decreased rates of SSI, anastomotic leak, and ileus in patients with IBD who received combined mechanical and oral antibiotic preparation prior to colectomy [72].

We believe that the evidence to support bowel preparation is not well established, and therefore, we recommend avoiding bowel preparation, but surgeons should be aware that ongoing studies might change this recommendation.

Evidence level III

Recommendations Mechanical bowel preparation prior to IBD surgery is not recommended.

Potentials for future researches Large multicenter RCTs investigating mechanical bowel preparation with and without perioperative AB compared with no mechanical bowel.

Treatment of comorbidity

The proportion of older patients among those with IBD is increasing, with a consequent increase in the complexity of comorbid conditions that require perioperative care [7, 73, 74]. A review by Kaplan et al. showed that comorbidities are common in patients with IBD, and they significantly increase the risk of postoperative mortality and healthcare use in this population [75]. Therefore, attention to correct these comorbidities prior to surgery is warranted.

Evidence level III.

Recommendations Comorbidities must be investigated and treated accordingly prior to IBD surgery.

Potential for researches Prospective multicenter cohort investigating the effect of well-treated comorbidities versus partly treated comorbidities in patients with IBD.

Smoking cessation

Smoking has a significant effect on the course of IBD. It is one of the most investigated environmental elements in patients with IBD, with alternating effects on CD and UC. Patients with CD who routinely smoke tobacco are at increased risk for strictures and fistulae leading to higher rates of bowel resection [76, 77]. There is also an increased risk for disease recurrence after surgery in patients with CD that are active smokers [78]. Smoking cessation can benefit the clinical course of CD [79]. On the other hand, smoking in UC seems to offer a protective effect when compared with patients who never smoked [80].

There is a fair amount of data about the effect of smoking and smoking cessation on the clinical course of IBD. However, only a few studies refer directly to the effect of smoking cessation on the surgical outcomes. In this review, we identified three articles describing postoperative complications, readmission, disease recurrence, and mortality in relation to preoperative smoking [81–83]. Sharma et al. reviewed over 47,000 patients undergoing colorectal surgery, including patients with IBD, and concluded that smokers have a

significantly increased risk for postoperative complications (OR 1.3; 95% CI 1.21–1.40) and overall mortality (OR 1.5; 95% CI 1.11–1.94) [83]. A subgroup analysis of 3770 patients with CD demonstrated that current smokers had a significantly higher risk of developing SSI (OR 1.27; 95% CI 1.01–1.59), infectious complications (OR 1.43; 95% CI 1.12–1.82), and major complications (OR 1.52; 95% CI 1.23–1.87) when compared with non-smokers. A review of observational studies about patients with CD concluded that smokers have an increased risk of surgical recurrence (OR 2.56; 95% CI 1.79–3.67; $P < 0.001$) and clinical recurrence (OR 2.15; 95% CI 1.42–3.27; $P < 0.001$) when compared to non-smokers [82]. A different result from another study on operated patients with CD where current smokers were compared with ex-smokers and non-smokers, demonstrated no differences in postoperative complications between the three groups [81]. However, the study suffered from different biases.

Evidence level III.

Recommendations All patients with IBD should be advised to stop smoking prior to elective surgery.

Potentials for future researches Up to date, no studies exist on the effect of preoperative smoking cessation on postoperative outcome in patients with IBD. RCTs or large prospective studies evaluating the effect smoking cessation on postoperative outcome in patients with IBD and timing of smoking cessation prior to surgery.

Discussion

Overall, there is no suffice evidence on the effect of PO on postoperative complications, length of postoperative stay, mortality, and readmission rates. In many areas, retrospective observational studies are dominant while large prospective studies and RCTs are generally lacking. Despite that, we believe that the recommendations provided by this systemic review (Table 2) could certainly be used to guide clinical decision-making and potential for future research. We must emphasize though that PO can only be effective in a multidisciplinary team approach, which appears to improve quality of care for IBD patients and to be cost-effective [20, 84–89]. Two of the PO factors that tackle chronic problems were included: treatment of comorbidities and cessation of smoking. The role of PO is not to correct the damage inflicted by a chronic process, but to ameliorate it. There is no reason to expect that patients with IBD deviate from other patients undergoing surgery regarding the beneficial effect of smoking cessation on wound healing despite lack of such studies.

Another PO factor, psychological support, was not discussed in this review due to the lack of evidence in preoperative setting. However, a review by Filipovic et al. [90] concluded that psychiatric therapy in patients with IBD is almost as important as the gastroenterological approach. Therefore, there is a foundation to include psychological support in any multimodel PO intervention.

Three reviews have earlier investigated the effect of PO on postoperative outcome in CD patients [18–20]. All studies contributed to raise attention about the important role of PO

Table 2 Summary of the recommendations for optimizing IBD patients prior to surgical intervention and the grade of evidence supporting these recommendations

Category	Recommendations	Level of evidence
Pharmacological considerations	• Preoperative steroid withdrawal is recommended.	IIb
	• Thiopurines preoperative are safe.	III
	• For elective surgeries, it may be prudent to plan the procedure remotely from the last dose of an anti-TNF agent, although the recommended duration of such delay is unclear.	III
Steroid stress dose	• If steroid withdrawal is not possible, the patients should continue to use their daily steroid dose preoperatively with no need for extra doses.	Ib
Nutrition	• Screening for malnutrition with a validated screening test for example NRS-2002.	III
	• Nutrition care plan for those at risk.	
Thrombosis prophylaxis	• Anticoagulants should be given to all patients with no obvious risk of bleeding.	III
	• If possible anticoagulants should be given 4 weeks postoperatively	IV
Treatment of preoperative sepsis	• Intra-abdominal abscess should be drained percutaneous using ultrasound guidance.	III
Prophylactic antibiotics	• Oral antibiotics should be given 24 h prior to surgery complementary to the perioperative IV antibiotics given (the evidence only counts for patients with ulcerative colitis).	II III
	• Longer preoperative treatment with antibiotics is not supported by evidence	
Mechanical bowel preparation	• Not supported by evidence.	III
Comorbidity	• Must be investigated and treated accordingly prior to surgery.	III
Smoking cessation	• Smoking stop is advisable when the patient is booked for elective surgery.	III

in IBD patients, although none included UC patients. Efron et al. and Sharma et al. did not have any methodological descriptions in their articles [18, 19] in contrast to Spinelli et al., which included a method section describing search strategy [20]. In this review, PRISMA guidelines were closely followed to ensure the clarity of reporting [91].

The authors chose to include all the important PO factors in one review for two reasons: first, to emphasize the multimodel approach to PO. A similar approach was suggested, investigated and became standard in postoperative enhanced recovery model. Secondly, there are reviews and meta-analyses in the different PO sections. In some PO factors, there are more than a handful meta-analyses. There is no need for extra meta-analyses of poor existing evidence, rather a study that highlights the gaps in our knowledge and paves the way for better-designed studies. Undoubtedly, bias assessment is essential for any systematic review but it does not fit in this review because of the heterogeneity in methodology and outcome reporting.

We chose to include all patients with IBD undergoing bowel surgery although there is more available evidence about PO in CD than in UC. Our review calls the attention for the vast unexplored area for researches in PO for patients with UC waiting for a definitive surgical treatment. Whether it is safe or not to make recommendations including these two disease entities is a matter of discussion. The inflammatory nature of these two diseases is still debated while difference in affected sites and smoking is an argument against. We choose to include only data from 2005 to July 31, 2015, to ensure up to date data. Selection bias was somewhat reduced by including reviews on individual PO factors. These reviews analyzed the older relevant data.

This review cannot and did not intend to generate evidence, but rather to critically examine the existing literature, attempt to narrow it to clear recommendations and point out the potentials for future research.

In conclusion, this review showed that PO plays an essential role in management of patients with IBD and highlighted gaps in our knowledge about the subject to stimulate future researches.

Contributions MZ and AE designed the study and developed the PRISMA protocol. All authors participated in literature reviews, analysis and interpretation of data, drafting the paper, and revising the manuscript. Literature search was done as follows: MZ (nutrition, thrombosis prophylaxis, treatment of preoperative sepsis), UK (preoperative medications), NH (prophylactic antibiotics, smoking cessation, bowel preparation), and AE (steroid stress dose, treatment of comorbidities). AE is the guarantor of the study. The paper was reviewed and edited for full professional proficiency in English.

Appendix. Search strategy from PubMed

((((((((((nutritional support) OR ((enteral nutrition) OR parenteral nutrition))) OR ((((((((((((((((((optimal preparation) OR optimisation) OR optimise) OR optimize) OR optimization) OR optimal preparation) OR preparation)) OR thrombosis prophylaxis) OR ((nutritional support) OR nutritional support[MeSH Major Topic])) OR nutritional support[MeSH Major Topic]) OR preoperative sepsis treatment) OR bowel rest) OR anticoagulants) OR nutritional support) OR period, preoperative) OR care, preoperative) OR ((sepsis therapy) OR sepsis treatment)) OR sepsis treatment) OR sepsis therapy))) AND ((surgery) OR colorectal surgery)) AND (Inflammatory bowel disease OR ibd OR Crohn disease OR crohn's disease OR Colitis ulcerative)))) OR (((((“inflammatory bowel diseases”[MeSH Terms] OR (“inflammatory”[All Fields] AND “bowel”[All Fields] AND “diseases”[All Fields]) OR “inflammatory bowel diseases”[All Fields] OR (“inflammatory”[All Fields] AND “bowel”[All Fields] AND “disease”[All Fields]) OR “inflammatory bowel disease”[All Fields]) OR ibd[All Fields] OR (“crohn disease”[MeSH Terms] OR (“crohn”[All Fields] AND “disease”[All Fields]) OR “crohn disease”[All Fields]) OR (“crohn disease”[MeSH Terms] OR (“crohn”[All Fields] AND “disease”[All Fields]) OR “crohn disease”[All Fields] OR (“crohn's”[All Fields] AND “disease”[All Fields]) OR “crohn's disease”[All Fields]) OR (“colitis, ulcerative”[MeSH Terms] OR (“colitis”[All Fields] AND “ulcerative”[All Fields]) OR “ulcerative colitis”[All Fields] OR (“colitis”[All Fields] AND “ulcerative”[All Fields]) OR “colitis ulcerative”[All Fields]))) AND ((((“surgery”[Subheading] OR “surgery”[All Fields] OR “surgical procedures, operative”[MeSH Terms] OR (“surgical”[All Fields] AND “procedures”[All Fields] AND “operative”[All Fields]) OR “operative surgical procedures”[All Fields] OR “surgery”[All Fields] OR “general surgery”[MeSH Terms] OR (“general”[All Fields] AND “surgery”[All Fields]) OR “general surgery”[All Fields]) OR (“colorectal surgery”[MeSH Terms] OR (“colorectal”[All Fields] AND “surgery”[All Fields]) OR “colorectal surgery”[All Fields])) OR (“postoperative complications”[MeSH Terms] OR (“postoperative”[All Fields] AND “complications”[All Fields]) OR “postoperative complications”[All Fields])) OR ((“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND (“infection”[MeSH Terms] OR “infection”[All Fields] OR “infections”[All Fields])))) AND (((((((“biological products”[MeSH Terms] OR (“biological”[All Fields] AND “products”[All Fields]) OR “biological products”[All Fields] OR “biologics”[All Fields]) OR “biological agent”[All Fields]) OR “biological agents”[All Fields]) OR (“biosimilar pharmaceuticals” [MeSH Terms] OR (“biosimilar”[All Fields] AND

"pharmaceuticals"[All Fields]) OR "biosimilar pharmaceuticals"[All Fields])) OR (((("infliximab"[MeSH Terms] OR "infliximab"[All Fields] OR "remicade"[All Fields]) OR ("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields] OR "humira"[All Fields])) OR (((((((("antibodies, monoclonal"[MeSH Terms] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibodies"[All Fields] OR ("antibodies"[All Fields] AND "monoclonal"[All Fields]) OR "antibodies, monoclonal"[All Fields]) OR ("PEG-modified tumor necrosis factor-alpha"[Supplementary Concept] OR "PEG-modified tumor necrosis factor- alpha"[All Fields] OR "peg modified tumor necrosis factor alpha"[All Fields])) OR "tumor necrosis factor-alpha/antagonists and inhibitors"[Mesh Terms]) OR (anti[All Fields] AND tnf[All Fields])) OR anti-tnf[All Fields]) OR ("adalimumab"[MeSH Terms] OR "adalimumab"[All Fields])) OR ("infliximab"[MeSH Terms] OR "infliximab"[All Fields]))))) OR ((((("steroids"[MeSH Terms] OR "steroids"[All Fields]) OR (("Stress"[Journal] OR "stress"[All Fields]) AND dose[All Fields])) OR ("glucocorticoids"[Pharmacological Action] OR "glucocorticoids"[MeSH Terms] OR "glucocorticoids"[All Fields])) AND scheme[All Fields])) OR (("comorbidity"[MeSH Terms] OR "comorbidity"[All Fields]) OR ("comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "comorbidities"[All Fields]))) OR ((("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "multidisciplinary"[All Fields]) OR (("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "multidisciplinary"[All Fields]) AND teamwork[All Fields])) OR (("interdisciplinary studies"[MeSH Terms] OR ("interdisciplinary"[All Fields] AND "studies"[All Fields]) OR "interdisciplinary studies"[All Fields] OR "multidisciplinary"[All Fields]) AND team[All Fields])))) OR (((((("Antibiotic Prophylaxis"[Mesh]) OR "Anti-Bacterial Agents"[Mesh])) OR (antibiotics OR "preoperative antibiotics" OR "anti bacterial prophylaxis"))) AND (((((("preoperative period" OR optimization OR preparation OR "optimal preparation" OR presurgery)) AND ("inflammatory bowel disease" OR IBD OR crohn's))) OR ((((("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh])) AND "Inflammatory Bowel Diseases"[Mesh])))) OR (((((((("psychological prehabilitation" OR "psychological interventon" OR "preoperative psychology")) OR ("mental support" OR "mental health" OR psycotherapy OR "psychological support"))) AND (((((("preoperative period" OR optimization OR preparation OR "optimal preparation" OR presurgery)) AND ("inflammatory bowel disease" OR IBD OR crohn's))) OR ((((("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh])) AND "Inflammatory Bowel Diseases"[Mesh])))) OR (((((((("preoperative period" OR optimization OR preparation OR "optimal preparation" OR presurgery)) AND ("inflammatory bowel disease" OR IBD OR crohn's))) OR ((((("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh])) AND "Inflammatory Bowel Diseases"[Mesh])))) OR (((((((("preoperative period" OR optimization OR preparation OR "optimal preparation" OR presurgery)) AND ("inflammatory bowel disease" OR IBD OR crohn's))) OR ((((("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh])) AND "Inflammatory Bowel Diseases"[Mesh])))) AND ("Smoking Cessation"[Mesh] OR smoking OR cigarette))))) OR (((((((("preoperative period" OR optimization OR preparation OR "optimal preparation" OR presurgery)) AND ("inflammatory bowel disease" OR IBD OR crohn's))) OR ((((("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh])) AND "Inflammatory Bowel Diseases"[Mesh]))) AND ("bowel preparation" OR "mechanical bowel preparation" OR "colonic preparation" OR "colonic clensing"))) Filters: Publication date from 2005/01/01 to 2015/07/31; Humans.

Results ➔ 2349 items.

Similar searches were conducted in EMbase and Cochrane Library. Exact search strategies for those databases can be requested if necessary.

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