

## Prehabilitation prior to intestinal resection in Crohn's disease patients: An opinion review

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**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Gangl A, Austria; Garg P, India

**A-Editor:** De Nardi P, Italy

**Received:** January 10, 2022

**Peer-review started:** January 10, 2022

**First decision:** March 8, 2022

**Revised:** March 21, 2022

**Accepted:** May 22, 2022

**Article in press:** May 22, 2022

**Published online:** June 14, 2022



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### Abstract

Patients with Crohn's disease (CD) are at a considerable risk for intestinal surgery. Approximately 25% of patients with CD will undergo an intestinal resection within 10 years of diagnosis. Postoperative complications after CD surgery have been reported in 20%-47% of the patients. Both general and CD-related risk factors are associated with postoperative complications, and comprise non-modifiable (e.g., age) and potentially modifiable risk factors (e.g., malnutrition). Prehabilitation focuses on the preoperative period with strategies designed to optimize

modifiable risk factors concerning the physical and mental condition of the individual patient. The aim of prehabilitation is to enhance postoperative recovery and return to or even improve preoperative functional capacity. Preoperative improvement of nutritional status, physical fitness, cessation of smoking, psychological support, and critical revision of preoperative use of CD medication are important strategies. Studies of the effect on postoperative outcome in CD patients are scarce, and guidelines lack recommendations on tailored management. In this opinion review, we review the current evidence on the impact of screening and management of nutritional status, physical fitness, CD medication and laboratory values on the postoperative course following an intestinal resection in CD patients. In addition, we aim to provide guidance for individualized multimodal prehabilitation in clinical practice concerning these modifiable factors.

**Key Words:** Crohn's disease; Prehabilitation strategies; Nutrition; Physical fitness; Medication; Laboratory values

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**Core Tip:** Nutritional status, medication, and laboratory values are modifiable factors that influence the postoperative course of patients with Crohn's disease. In addition, physical fitness is impaired in the perioperative course and therefore preoperative screening is warranted. Individualized multimodal prehabilitation programs aim to improve these modifiable risk factors before surgery, including smoking cessation and psychological screening and support, and should be integrated in the preoperative preparation period in order to reduce both postoperative complications and undesirable outcomes.

**Citation:** Bak MTJ, Ruitkamp MFE, van Ruler O, Campmans-Kuijpers MJE, Bongers BC, van Meeteren NLU, van der Woude CJ, Stassen LPS, de Vries AC. Prehabilitation prior to intestinal resection in Crohn's disease patients: An opinion review. *World J Gastroenterol* 2022; 28(22): 2403-2416

**URL:** <https://www.wjgnet.com/1007-9327/full/v28/i22/2403.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v28.i22.2403>

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by segmental, transmural inflammation, which most commonly affects the ileum and/or colon[1]. Although the risk of intestinal resection and re-resection has declined considerably over the past decades, approximately 25% of patients will undergo an intestinal resection within 10 years of CD diagnosis[2,3].

An intestinal resection is potentially perceived as a major life event and has a significant psychological impact on CD patients, which can result in anxiety and depressive symptoms in the pre- and postoperative setting[4]. Despite the immediate relief of symptoms and a potential increase of quality of life after CD surgery[5], important concerns are the risk of potential (severe) complications and recurrence of CD[6]. Reports on the frequency of postoperative complications, following intestinal resection in CD patients, range from 20%-47%[7-12]. Several general and CD-specific risk factors for postoperative complications have been identified. Both non-modifiable risk factors (*i.e.*, comorbidity, older age) and modifiable risk factors (*i.e.*, malnutrition, preoperative medication use, abnormal preoperative laboratory values and smoking) have been associated with postoperative complications[8-10,12,13]. In addition, preoperative physical fitness, specifically aerobic fitness, seems impaired in patients with CD[14], which may increase the risk for adverse postoperative outcomes as has been observed in colorectal cancer (CRC) surgery[15,16].

Prehabilitation focuses on the preoperative period by suggesting strategies designed to optimize modifiable risk factors concerning the physical and mental condition of the individual patient. As such, prehabilitation aims to improve the postoperative course and promotes an earlier postoperative recovery and return to functional capacity[6]. A four-pillar multimodal prehabilitation program tailored to the individual patient involves improving: (1) Physical; (2) Nutritional; (3) Psychological status; and (4) Cessation of smoking, resulted in a significant earlier recovery to the baseline functional capacity in patients with CRC[17]. In addition, preoperative physical exercise training to improve aerobic fitness significantly reduced postoperative complications in high-risk patients, both in general[18] and those with CRC[19], undergoing abdominal surgery as compared to usual care. These programs may also benefit patients in other settings of abdominal surgery, including CD[20]. However, literature on prehabilitation in CD patients scheduled for intestinal resection is scarce and guidelines lack recommendations on tailored management[21,22].

**Table 1 Recommendations on screening for prehabilitation prior to intestinal surgery in Crohn's disease**

Screening	
Nutritional status	Screening in all patients: Body mass index, evaluation of unintentional weight loss and assessment of dietary intake with nutritional or immunological screening tools ( <i>e.g.</i> , GLIM and OPNI). Preferably assess the muscle mass ( <i>e.g.</i> , with handgrip strength or consider available imaging techniques) to complement the measures of nutritional status
Physical fitness	Screening in all patients to estimate aerobic fitness with validated self-reporting questionnaire ( <i>e.g.</i> , Duke activity status index, veterans-specific activity questionnaire). Consider referral of patients at risk for impaired physical fitness for comprehensive objective assessment by an exercise specialist
CD medication	Critically revise all current CD medication on a case-by-case basis
Laboratory assessment	Preoperative assessment of full blood count, CRP, and serum albumin. Assessment of vitamins and other trace elements may only be indicative in patients with biochemical remission
Smoking psychological status	Screen all patients on active smoking  Discussion of expectations and potential fears for the perioperative course by treating physicians IBD team members

CD: Crohn's disease; CRP: C-reactive protein; GLIM: Global Leadership Initiative on Malnutrition; IBD: Inflammatory bowel disease; OPNI: Onodera's prognostic nutritional index.

**Table 2 Recommendations for prehabilitation interventions prior to intestinal surgery in Crohn's disease**

Intervention	
Nutritional	Nutritional support may be considered in case of impaired nutritional status and/or inadequate intake with regard to proteins and calories. Minimum duration of nutritional support is 1-2 wk and may be extended to 6-8 wk to fully benefit from the dietary intervention. EEN may be considered as nutritional support for immunomodulatory effect and reduction of postoperative complications. TPN seems a valid option only when enteral nutrition is contraindicated, not effective or tolerated
Physical fitness	Physical exercise aerobic activity and muscular resistance training may be considered to improve physical fitness in the preoperative course. High-intensity physical exercise should be avoided due to risk of exacerbation of inflammation and symptoms
CD medication	Wean off corticosteroids to a minimal dose (preferably < 20 mg) 6 wk prior to surgery. Consider cessation of anti-TNF- $\alpha$ agents (especially in case of therapy-refractory disease). If considered, a time-interval of 4 wk (ADA) or 6-8 wk (IFX) seems appropriate
Laboratory assessment	Preoperative intravenous iron therapy is recommended in case of iron deficiency anemia in the preoperative course. In case of hypoalbuminemia and an impaired nutritional status, nutritional support is advised (see nutritional and physical status)
Smoking	Preoperative cessation is recommended ( <i>e.g.</i> , within smoking cessation program)
Psychological status	Provide individualized psychosocial support or refer to psychologist

CD: Crohn's disease; ADA: Adalimumab; EEN: Exclusive enteral nutrition; IFX: Infliximab; TNF- $\alpha$ : Tumor necrosis factor-alpha; TPN: Total parenteral nutrition.

In this opinion review, the available literature on the effect of potentially modifiable preoperative factors on the postoperative course following an intestinal resection in CD is critically appraised, with a focus on nutritional status, physical fitness, CD medication, and laboratory values. In addition, we aim to provide guidance for screening and specific interventions on these items during the preoperative course of patients with CD (Tables 1 and 2). Although psychological screening and support, as well as smoking cessation are considered essential during preoperative optimization in CD, these topics will not be addressed in this review. For these topics, management in accordance with general guidelines and integration into a multimodal prehabilitation program is recommended.

## METHODS

A literature search of the EMBASE, Medline, Web of Science, Google Scholar and Cochrane Library databases was conducted, in collaboration with the Medical School Library of the Erasmus University Rotterdam. High-quality articles were cited in Reference Citation Analysis (RCA) (<https://www.referencecitationanalysis.com>). The following keywords, synonyms and their Medical Subject Headings terms were used for this search: 'Crohn's disease', 'intestinal surgery', and 'risk factors' (Supplementary material).

Studies published in the English language up to July 2021 were considered according to their topical relevance for the impact of screening and management of nutritional status, physical fitness, CD medication and laboratory values in the preoperative period related to the postoperative course

following an intestinal resection in CD patients. In the case that no relevant studies were present virtually for any of these topical contents, the literature was re-assessed in other settings of abdominal surgery (*e.g.*, patients with CRC). Only randomized controlled trials, meta-analyses, systematic reviews, observational studies (case-control study and patient series without control) were selected. Study selection was independently performed by both two reviewers (Bak MTJ and Ruitkamp MFE) based on title and abstract. The snowball method was then applied to all of the final selected studies.

## HOW TO SCREEN AND OPTIMIZE THE NUTRITIONAL STATUS AND PHYSICAL FITNESS OF PATIENTS WITH CD PRIOR TO INTESTINAL RESECTION?

### **Preoperative screening of nutritional status**

Malnutrition is an important risk factor for a dismal postoperative course after intestinal resection in CD [23]. Malnutrition encompasses undernutrition and overnutrition. CD patients are prone to undernutrition due to inadequate nutritional intake attributable to several causes (*e.g.*, anorexia, strictures), malabsorption (*e.g.*, active inflammation or after prior resection) and chronic inflammation. However, obesity in the CD population has increased over the years[24]. Recognition of nutritional status as the key issue in preoperative optimization for patients with CD is gaining ground, since a significant benefit from dietary intervention may not only be expected after optimization of the nutritional status but also from its potential immunomodulatory effect on CD.

A first screening for malnutrition is readily available to all caregivers treating patients with CD and is recommended in all preoperative CD patients according to current guidelines[21-23]. Since a survey among 146 gastroenterologists in 2016 revealed that one-third of respondents did not routinely screen for malnutrition, exploration of the reasons for non-adherence is required[25]. The initial nutritional assessment during preoperative screening requires a combination of: (1) Body mass index (BMI); (2) Evaluation of unintentional weight loss; and (3) Assessment of dietary intake. Assessment of muscle mass preferably complements these measures. Laboratory assessment of albumin and micronutrients is not a reliable marker of malnutrition, and will be addressed in a later paragraph[23].

BMI is a commonly used indicator for body fat and thus a proxy of nutritional status. Preoperative BMI value and the rate of postoperative complications are only moderately correlated, according to abundant reports[26-30]. Nevertheless, clearly underweight patients, defined with varying cut-off values in the literature (from BMI < 16.2 kg/m<sup>2</sup> to BMI < 18.5 kg/m<sup>2</sup>), are at an increased risk of a dismal postoperative course after intestinal resection, including creation of an ileostomy[9], readmission[31], intra-abdominal septic complications (IASCs)[32], and overall postoperative complications[33,34]. Similarly, clearly overweight patients suffering from obesity, defined as a BMI cut-off > 30 kg/m<sup>2</sup>, also face an elevated risk of complications[9,28,34-36]. In addition, another study reported an increasing BMI by 1 unit (U) associated with an increased risk [odds ratio (OR) = 1.04; 95% confidence interval (CI): 1.0-1.1; *P* = 0.008] of postoperative complications[35].

Unintentional preoperative weight loss may occur in all CD patients independent of their baseline weight. Various studies assessing the effect of preoperative weight loss have confirmed the association with postoperative complications in CD patients. Unintentional weight loss of > 10%, as compared to baseline over the last 6 mo prior to surgery, is a commonly described cut-off[9,10,36-38]. This cut-off of significant weight loss has been observed in 23%-54% of CD patients scheduled for intestinal resection [23]. Various studies have reported a clear negative association between recent unintentional weight loss and postoperative complications in CD patients[9,10,36-38].

In addition, other measures of body composition may warrant evaluation during the preoperative assessment. The most important is sarcopenia, which is defined as low lean muscle mass in combination with either low muscle strength or low physical performance[39]. Sarcopenia can be present in both under- and overweight individuals[40]. Moreover, sarcopenia is common in CD patients, with a reported overall incidence of 52%, as determined by radiologic assessment of body mass composition (*e.g.*, skeletal mass index, total psoas index and/or Hounsfield U average calculations at the level of the third lumbar vertebral body)[40,41]. A recent meta-analysis identified sarcopenia as an independent predictor for both postoperative complications and/or undesirable outcomes (*i.e.*, poor quality of life, inadequate response to therapy) in the IBD population[42]. Especially in patients younger than 40 years, sarcopenia was a strong and independent risk factor for postoperative complications, and patients with a low or normal BMI were affected more often[43]. Handgrip strength is an accessible and reliable diagnostic method for sarcopenia applied in routine practice. When sarcopenia in CD patients is detected in the preoperative setting, a combined intervention to optimize the closely related nutritional status and improved physical fitness may enhance postoperative prognosis[44]. However, data on these specific interventions are lacking.

To date, several nutritional screening tools are available to assess the nutritional status in the IBD population. These tools combine such clinical features as BMI, weight loss, and symptoms (for instance diarrhea). Amongst these tools are the following: Nutrition Risk Screening (NRS-2002)[45]; Malnutrition Universal Screening Tool (MUST)[46]; Global Leadership Initiative on Malnutrition (GLIM) criteria[47]; and more IBD-specific tools, such as the Malnutrition Inflammatory Risk Tool (MIRT)[48] and Saskat-



chewan IBD Nutrition Risk Tool[49]. The GLIM has a higher rate of malnutrition detection in preoperative IBD patients as compared to several other screening tools (namely NRS-2002, MUST, MIRT, and Saskatchewan IBD Nutrition Risk Tool)[50]. Moreover, chronic inflammation is used as an indicator in this nutritional screening tool[47]. The Onodera's prognostic nutritional index (OPNI) is a simple and useful index to merely reflect the preoperative immunological status using serum albumin level and total lymphocyte counts. OPNI predicts the risk of postoperative complications in various types of cancer[51]. Limited data of the prognostic value of the OPNI in CD suggests that OPNI < 40 is a predictor of infectious complications or postoperative abdominal bleeding[52-54]. Overall, more data on the association between malnutrition detected by these screening tools and the postoperative course are required to support their routine use.

### **Future nutritional screening methods**

An altered body composition is a known risk factor for postoperative complications[23]. Current available imaging techniques provide the opportunity to screen the body composition and develop new nutritional predictors for postoperative outcome. Although cross-sectional imaging with the sole purpose of evaluating body composition is not indicated, and available scans may be used for objective evaluation. Visceral fat promotes both local and systemic inflammation, resulting in a chronic inflammatory status[55,56]. Increased[57] and decreased[58] subcutaneous fat as well as increased visceral fat [59] are associated with increased risk of early postoperative complications in CD patients. Moreover, an expanded visceral/subcutaneous fat ratio (VSR) was identified as a better predictor of the postoperative outcome compared to BMI[58]. However, another study reported no association between VSR and postoperative complications[60]. In addition, there seems to be different cut-off points of total subcutaneous fat for CD patients, compared to other patients[57]. Therefore, these promising markers warrant further investigation.

### **Preoperative screening of physical fitness**

To date, there is no routine screening for physical fitness in patients with CD in the preoperative course. In general, the physical fitness of CD patients is impaired[14,61]. Two cross-sectional studies concluded that physical fitness, specifically aerobic fitness, is impaired in the perioperative course of patients with CD as compared to the general population or other subgroups undergoing abdominal surgery[14,62]. This impairment is attributed to a lack of physical activity due to illness behavior and/or impaired nutritional status affecting muscle function[14,61,63,64]. More objective insights into the level of physical fitness in patients with CD are required, as well as into the association between physical fitness and patient-, disease-, and treatment-related outcomes. The specific subgroups of patients with impaired aerobic fitness may benefit most from a targeted and personalized physical exercise intervention. A validated self-reporting questionnaire (*e.g.*, Duke activity status index, veterans-specific activity questionnaire) may serve as a simple screening tool to identify patients with impaired aerobic fitness[65,66]. These patients may receive a comprehensive objective assessment by an exercise specialist (*e.g.*, physical therapist, clinical exercise physiologist) to evaluate the specific exercise intolerance and propose a personalized prescription for physical exercise training.

A cardiopulmonary exercise test is considered the gold standard for assessing aerobic fitness and also provides valuable information to determine physical exercise training safety (*e.g.*, contraindications) by assessing the body's integrated physiological response to progressive exercise[67]. Moreover, cardiopulmonary exercise test results can be used to optimize and personalize training intensity. When performance of a cardiopulmonary exercise test is not possible, a more practical performance-based field test to evaluate a patient's aerobic fitness can be used. The steep-ramp test is a short time maximal exercise test on a cycle ergometer, of which its primary outcome parameter (the achieved peak work rate) is highly correlated with aerobic fitness indicators obtained at the cardiopulmonary exercise test [68].

Low- to moderate-intensity physical exercise training interventions are feasible and safe in IBD patients in the non-perioperative setting, and have been associated with improved physical fitness as well as with a significant reduction of (severe) fatigue and stress, and a significant improvement of quality of life[69-71]. To date, no preoperative physical exercise training studies have been conducted in patients with CD. As aerobic and resistance training have been found to be effective for the reduction of postoperative complications and accelerates recovery of functional capacity in unfit patients undergoing abdominal surgery[18,19], patients with CD may benefit from these interventions as well in the preoperative course[72]. It seems that high-intensity physical exercise training should be avoided, as it may lead to an acute exacerbation of inflammation and CD symptoms[73]. Overall, future research for the effect of physical interventions on the preoperative course of CD patients is warranted.

### **Preoperative optimization of nutritional status**

To reverse the negative impact of malnutrition on the postoperative course in CD patients, preoperative optimization of the nutritional status is indicated. The European Society of Clinical Nutrition and Metabolism (ESPEN) states that the preoperative optimization of the nutritional status by enteral nutrition (EN) for 7-10 d, in the case of mildly malnourished patients, or 7-14 d in the case of a severe nutritional risk, is appropriate[74]. Nutritional support is administered enterally, and only parenteral in

case EN has failed or is contraindicated (*e.g.*, due to an intestinal obstruction)[74].

A Cochrane review on preoperative nutritional support in patients scheduled for gastrointestinal surgery reported a significant reduction of anastomotic leakage and need for a temporary diverting stoma [overall risk ratio (RR) = 0.67; 95%CI: 0.53-0.85][75]. In line with these findings, a meta-analysis showed that preoperative nutritional therapy significantly reduces postoperative complications in patients with CD (OR = 0.26; 95%CI: 0.07-0.99)[76]. In particular, EN was superior to usual care (defined as no nutritional support) (OR = 0.09; 95%CI: 0.06-0.013)[76,77]. A trend towards superiority of total parenteral nutrition (TPN) as compared to standard care was observed, but statistical significance was not reached[76].

Exclusive EN (EEN) consists of complete liquid diet of various compositions and has been widely used as induction therapy in pediatric CD patients with a duration of 6 wk to 8 wk[78,79]. EEN is effective as preoperative therapy by inducing both clinical and histological remission in adult CD patients[80,81]. The anti-inflammatory effect of EEN can be attributed to the reduction of mucosal cytokines and composite alterations of the gut microbiome[81,82]. Cohort studies, which investigated the effect of EEN in the preoperative setting in the CD population, demonstrated a significant reduction in overall postoperative complications[83-85], IASCs[86,87], and postoperative abscesses and anastomotic leakage[80,86,88]. Moreover, EEN has proven to be beneficial in the reduction of C-reactive protein (CRP)[80,83-85] and the increase of albumin, OPNI, and hemoglobin level[83,84].

In case EN fails or is contraindicated, PN is suggested. PN can be divided into partial PN (PPN) and TPN. PN is administered into the venous system *via* a catheter into the superior vena cava or a peripherally-inserted central catheter. Patients treated with TPN only receive a completely intravenous (IV) nutritional liquid diet, while patients with PPN may receive nutrients from other sources alongside PN. The literature on the effect of PN on postoperative complications following intestinal resection in CD is scarce. Available studies reported a significant decrease in overall postoperative complications [89], non-infectious complications[90], anastomotic leakage[88], and the length of the resection specimen [91]. Benefits of TPN were observed in patients who were treated with TPN for  $\geq 60$  d[90] or for the duration of 18-90 d[89]. However, the benefit of PN as nutritional support needs to be weighed against the possible risk of catheter-related infections[92].

### Reviewers' opinion

In summary, since extremes in BMI ( $< 18.5$  kg/m<sup>2</sup> or  $> 30$  kg/m<sup>2</sup>) and recent unintentional weight loss ( $> 10\%$  within 6 mo prior to surgery) have been associated with a dismal postoperative course in CD patients, we recommend the assessment of both in the preoperative setting. The detection of significant unintentional weight loss is a red flag and postponement of the intestinal resection until after restoration of the catabolic status should be considered. Moreover, assessment of handgrip strength may be used to detect sarcopenia. We consider GLIM as an appropriate screening tool for malnutrition in CD patients as chronic inflammation is included as one of the indicators. Moreover, the GLIM had a higher detection rate of malnutrition as compared to other screening tools in preoperative IBD patients. In addition, the OPNI can be used as an immunological screening tool. However, the prognostic value of these tools on the postoperative course requires further research. In our opinion, nutritional support during preoperative optimization may be considered for all patients with either an impaired nutritional status and/or inadequate intake with regard to proteins and calories. After a diagnosis of malnutrition, an individualized window to surgery needs to be decided to optimize nutritional status. As physical fitness is impaired in CD and therefore may influence the postoperative course, preoperative screening is warranted with use of self-reporting questionnaires. In addition, patients at risk may benefit from an objective assessment to evaluate specific exercise intolerance and a personalized prescription for physical exercise training. When pre- and postoperative physical fitness is impaired in patients with CD, aerobic and resistance training are recommended. The optimization period as suggested by the ESPEN (7-14 d) may be considered a minimum and, after careful evaluation per individual case, be extended up to 6-8 wk in most cases to fully benefit from the dietary intervention. EEN seems a promising preoperative nutritional intervention to improve prognosis due to its immunomodulatory effect, especially in patients with penetrating CD complications. Nutritional support is administered enterally (oral or *via* a nasogastric tube) (*i.e.*, EN), and only in exceptional situations parenterally (when enteral nutritional support fails). TPN seems a valid option only when EN is contraindicated, not effective, more tolerable.

## WHAT IS THE OPTIMAL TIMING TO DISCONTINUE CD MEDICATION PREOPERATIVELY?

CD-related medication has an immunomodulatory effect and may increase the risk of infections. This may also result in postoperative surgical site infections (SSIs) and/or IASCs. The European Crohn & Colitis Organization (ECCO) guideline recommends to wean off corticosteroids 6 wk before surgery [21], while the guideline of the British Society for Gastroenterology (BSG) recommends to stop corticosteroids or minimize the dose, without specifying a window to surgery[22]. Moreover, the BSG recommends cessation of infliximab and adalimumab 6-8 wk and 4 wk prior to surgery, respectively

[22], whereas the ECCO guideline states that cessation of anti-tumor necrosis factor- $\alpha$  (TNF)- $\alpha$  therapy prior to surgery is not mandatory[21].

A recent Cochrane review studied the potential impact of perioperative IBD medication on the risk of postoperative (infectious) complications within 30 d in IBD patients[93]. The pooled data of this meta-analysis reported a significant association of corticosteroids with the risk of overall infectious postoperative complications (OR = 1.70; 95%CI: 1.38-2.09) and intra-abdominal infections (OR = 5.95; 95%CI: 1.04-34.1) in CD patients[93]. Furthermore, a significant increased risk of overall infectious complications (OR = 1.60; 95%CI: 1.20-2.13) was observed in patients treated with an anti-TNF- $\alpha$  agent [93]. No significant association was reported for patients who received the last dose of anti-TNF- $\alpha$  more than 8 wk before surgery[93]. However, these results should be interpreted with caution since the evidence for all outcomes was of low or very low quality, mostly due to the observational design, heterogeneity, and risk of bias of the included studies[93].

Pooled data of that meta-analysis demonstrated no significantly increased risk of overall postoperative infectious complications in CD patients treated with immunomodulatory, anti-interleukin and anti-integrin therapy[93]. Nevertheless, two retrospective studies have found a significant association of thiopurines, in combination with anti-TNF- $\alpha$  or corticosteroids, with IASC and overall infectious complications in the postoperative course[94,95]. The relation between vedolizumab, an anti-integrin agent, and postoperative complications has been studied in nine observational cohort studies including a total number of 799 patients and predominantly evaluating patients who underwent abdominal surgery with overall postoperative (infectious) complications as the primary endpoint[29,96-102]. Two studies found a significant increased risk of SSIs in patients treated with vedolizumab in the preoperative course[29,96]. Another study reported a significant decreased risk of postoperative ileus in CD patients with detectable vedolizumab levels as compared to non-detectable vedolizumab levels[99]. Four observational studies found the outcomes of preoperative ustekinumab use on postoperative complications and infectious complications, and found no significantly increased risk[96-98,103].

### Reviewers' opinion

In accordance to the current literature and guidelines, we would recommend to wean off corticosteroids to a minimal dose, preferably < 20 mg, 6 wk prior to surgery. Moreover, cessation of anti-TNF- $\alpha$  agents may be considered, especially in non-responders and/or therapy refractory CD. When cessation is considered, a time interval of 4-8 wk (depending on type of anti-TNF- $\alpha$  agent) prior to surgery seems appropriate. Although the evidence on an association with increased risk of infections is unclear for other CD-medication, critical revision of the benefit of continuation until the date of surgery is indicated in all patients on an individual basis. In addition, since the biologic effect may last longer and vary per agent from 1 mo (prednisolone < 10 mg) to 3 mo (immunomodulators, anti-TNF- $\alpha$ ) or longer (vedolizumab and ustekinumab), data on the effect of intervention are required to prove the beneficial effect of timely cessation[104].

## WHICH LABORATORY VALUES ARE ASSOCIATED WITH THE POSTOPERATIVE COURSE AND NEED TO BE ASSESSED PRIOR TO INTESTINAL RESECTION IN PATIENTS WITH CD?

Specific recommendations concerning the preoperative assessment of laboratory values in CD patients are lacking in the BSG and ECCO guidelines[21,22]. Nevertheless, abnormal laboratory values in the preoperative setting have been associated with a dismal postoperative course in CD. Hypoalbuminemia (defined as serum albumin < 30 g/L) is one of the criteria for the diagnosis of (severe) malnutrition in general[74]. However, albumin is an acute-phase reactant protein and serum levels may decrease due to active inflammation[23]. Probably due to the chronic inflammatory state, serum albumin levels are lower in CD patients, as compared to the general population, and are reversely correlated to the disease activity[105]. Therefore, serum albumin is not a reliable marker for malnutrition in CD. Nevertheless, low serum albumin (ranging from < 29 g/L to 35 g/L) is associated with an increased risk of postoperative complications in CD patients[10,102,106-108]. These complications comprised overall early post-operative complications (< 30 d)[60,102,109-111], IASCs[10,106,112,113], SSIs[107,114], anastomotic leakage[88], and infectious complications[33,108,115].

Assessment of a full blood count, including hemoglobin and leucocyte and platelet counts, is advised in patients undergoing elective abdominal surgery[116]. The most important test seems to be that for hemoglobin, as anemia is present in up to 78% of patients requiring a surgical intervention[117]. Both a preoperative anemia (defined as < 10 g/dL)[9,37,106,108,118] and a lowered hemoglobin level (defined as lower than the reference value)[27,38,102,119] are associated with postoperative complications in CD patients. Iron deficiency anemia is the most common cause of anemia in the preoperative setting of CD. Preoperative IV iron therapy is highly effective to rapidly increase hemoglobin levels, and should be considered the first choice. Blood transfusion is a common practice to treat anemia when treatment for the underlying cause has been unsuccessful. Both intra- and perioperative blood transfusions have been

associated with infectious- and/or non-infectious postoperative complications in CD patients, whereas a preoperative blood transfusion was not associated with postoperative complications[120-123].

Elevated levels of the inflammatory markers (*i.e.*, leucocyte count) are risk factors for postoperative complications[30,120,121,124]. Furthermore, a preoperative elevated CRP level has been associated significantly with overall postoperative complications[52,125-127], infectious complications[33,57,125-127], and SSIs[57]. It is known that the malabsorption of vitamins and other trace elements is prevalent in CD patients. Plasma concentrations are influenced by active disease or result from earlier intestinal resections. These micronutrient deficiencies comprise several vitamins (most often B6, B12, D, and K), iron, folic acid, selenium, and zinc. Micronutrient deficiencies are associated with a complicated course of disease[128]. For reliable assessment of body micronutrient status, the patient needs to be in biochemical remission. However, in cases of high suspicion due to deficiency-related complaints or malnutrition, assessment of these values is indicated[23,128].

### Reviewers' opinion

Although preoperative anemia, hypoalbuminemia, elevated CRP and elevated leucocyte count are associated with postoperative complications, CD-specific recommendations concerning the preoperative assessment of laboratory values and subsequent management cannot be derived from the current literature. Laboratory findings for vitamins and other trace elements are often disturbed in CD and may not reflect the actual nutritional status. These assessments only reflect the patient's nutritional status when a patient is in remission. We recommend to assess full blood count, CRP and serum albumin preoperatively as predictive markers of a complicated postoperative course and to preoperatively correct iron deficiency anemia, in accordance with the ECCO guideline[21].

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## CONCLUSION

Nutritional status, medication and laboratory values are modifiable factors that influence the postoperative course of patients with CD. In addition, physical fitness is impaired in CD patients and may impact postoperative outcomes. As a lower preoperative physical fitness is associated with a higher risk for postoperative complications in other populations undergoing intestinal resection, further research into interventions in CD patients is warranted. Individualized multimodal prehabilitation programs aim to improve these modifiable risk factors before surgery, including smoking cessation and psychological screening and support, and should be integrated in the preoperative preparation period in order to reduce both postoperative complications and undesirable outcomes.

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## ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of Wichor Bramer, biomedical information specialist of the Erasmus University Medical Center, for performing the systematic literature search.

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## FOOTNOTES

**Author contributions:** Bak MTJ reviewed and summarized the literature, and drafted the article; Ruitkamp MFE reviewed the literature; de Vries AC supervised the study; and all authors contributed substantially to the concept and design of the study, critically revised the article, and approved the final version.

**Conflict-of-interest statement:** van der Woude CJ received grants and or fee for advisory boards and presentations from Pfizer, Abbvie, Celltrion, Falk Benelux, Takeda, Janssen, and Ferring outside the submitted work; de Vries AC has served on advisory boards for Takeda, Janssen, Bristol Myers Squibb, Abbvie, Pfizer, and Galapagos and has received unrestricted research grants from Takeda, Janssen, and Pfizer outside the submitted work; and all other authors declare that they have no conflict of interest.

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**S-Editor:** Wang JJ

**L-Editor:** A

**P-Editor:** Wang JJ

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