

# Preoperative Enteral Nutrition and Surgical Outcomes in Adults with Crohn's Disease: A Systematic Review

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## Keywords

Crohn's disease · Enteral nutrition · Adults · Surgery · Preoperative · Postoperative · Morbidity · Complications

## Abstract

**Background and Aim:** Enteral nutrition (EN) is applicable to adult Crohn's disease (CD) in treating malnutrition and in inducing remission – here as a less effective alternative than corticosteroids. The purpose of this review is to determine whether preoperative EN impacts postoperative complications of adult CD, either by means of nutritional or therapeutic effects. **Summary:** A systematic review of English written full-text research articles published between January 1990 and November 2017, including adult patients undergoing abdominal surgery for complicated CD after EN, was performed. Four studies out of 22 were selected, all of which institutional, retrospective, case-control cohorts, one classified as “good quality” and three as “poor quality,” as rated by

the Newcastle-Ottawa Scale. The application of inclusion and exclusion criteria resulted in a non-intentional absence of studies referring to supplemental EN among those reviewed. The reduced number of heterogeneous eligible studies impeded meta-analysis. In all studies, exclusive EN (EEN) was used and well tolerated, allowing to defer or even avoid surgery altogether, improving patients' global state. The two studies with the greatest number of patients found preoperative EEN to be an independent factor against infectious and non-infectious complications in 219 patients and against anastomotic leaks or abscesses in 38 patients. Also, in univariate analysis, EEN was found to increase preoperative immunosuppressant-free intervals and to protect against anastomotic dehiscences, intra-abdominal abscesses, surgical wound infections, ileus, stomas, and reoperations in the largest study; in another study it was related to fewer intra-abdominal septic complications. **Key Messages:** All reviewed studies are retrospective and, consequently, of limited relevance. Nonetheless, all of them call the attention

of the scientific community to the potential benefits of pre-operative EEN on postoperative outcomes in adult CD, calling for prospective multi-institutional studies and randomized controlled trials.

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## Nutrição entérica pré-operatória e resultados pós-operatórios em adultos com doença de Crohn: revisão sistemática

### Palavras Chave

Doença de Crohn · Nutrição entérica · Adultos · Cirurgia · Pré-operatório · Pós-operatório · Morbilidade · Complicações

### Resumo

**Introdução e objetivo:** No adulto com doença de Crohn (DC) a nutrição entérica (NE) é aplicável como terapêutica da desnutrição ou como alternativa, menos eficaz, aos corticoides, para indução de remissão. O objetivo desta revisão é determinar se a NE pré-operatória tem impacto nas complicações pós-operatórias, seja pelo efeito nutricional seja pelo terapêutico. **Sumário:** Foi realizada uma revisão sistemática dos artigos de investigação que incluíssem doentes adultos submetidos a cirurgia abdominal por DC complicada, após NE, redigidos em inglês e publicados entre janeiro de 1990 e novembro de 2017. De 22 estudos foram selecionados quatro institucionais e retrospectivos de coorte, um de “fraca qualidade” e três de “pobre qualidade” pela “Newcastle-Ottawa Scale”. Nos estudos revistos foi utilizada NE exclusiva (NEE) já que, não intencionalmente, os estudos com NE suplementar reuniram critérios de exclusão. O pequeno número e a heterogeneidade dos estudos elegíveis impossibilitaram uma meta-análise. A NEE foi utilizada e bem tolerada em todos os estudos, e permitiu melhorar o estado global dos doentes e protelar ou mesmo evitar a cirurgia. Nos dois estudos com maior número de doentes, a NEE pré-operatória foi um fator independente contra deiscências de sutura e abscessos em 219 doentes, e contra complicações infecciosas intra-abdominais em 38. Em análise univariada também se verificou que, no maior estudo, a NEE aumentou o intervalo pré-operatório livre de imunossupressores e foi protetora contra deiscências anastomóticas, abscessos intra-abdominais, infeções da ferida operatória, ileus, estomas e reoperações; noutro estudo menores correlacionou-se com menos complicações infecciosas intra-ab-

dominais. **Mensagens-chave:** Todos os estudos revistos são retrospectivos e, conseqüentemente, de relevância limitada. No entanto, todos chamam a atenção da comunidade científica para os potenciais benefícios da NEE pré-operatória nos resultados pós-operatórios dos adultos com DC e para a necessidade de estudos prospectivos multi-institucionais e de ensaios clínicos randomizados.

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### Introduction

Up to 50% of Crohn’s disease (CD) patients have been classically described to require surgery within 10 years after diagnosis [1]. More recently, according to a population-based cohort study from Denmark, the 9-year cumulative risk of surgery has been reduced from 50% (1979–1986) to 23.3% (2003–2011), along with an increased use of thiopurines and TNF $\alpha$  inhibitors [2]. The same trend was found in a similar study from Sweden – the risk of surgery at 5 years fell from 65.8% (1963–1975) to 34.6% (1991–2005) [3].

Rates of postoperative complications and stoma creation after abdominal surgery are influenced by a number of factors, both clinical and therapeutic, and vary widely across published series [4, 5]. Intra-abdominal septic complications (IASCs) may reach 50%, the risk factors for which the literature mostly reports therapy with corticosteroids (CSTs), malnutrition, intra-abdominal abscesses, low serum albumin levels, and emergent surgery [6–11].

Among medications used in the treatment of CD, CSTs are the one most consensual risk factor for anastomotic complications and, in some series, for global morbidity [4, 6, 9, 10]. As to purine analogues, there is no evidence they might increase the risk of postoperative complications [9, 11, 12]. Differently, TNF $\alpha$  inhibitors increase infectious and global surgical morbidity [11, 13–15].

In what concerns preoperative malnutrition, undernourished CD patients should receive perioperative nutritional support, as in other pathologies of the digestive tract, even if this requires postponing surgery. The enteric route is preferred, whereas parenteral nutrition (PN) is only indicated when the digestive tract is insufficient or unavailable [16–19]. Whenever the digestive tract does not provide enough calories – in patients who tolerate enteral nutrition (EN) but in insufficient quantities – the use of total or supplementary PN becomes inevitable [16]; operating undernourished patients, with consequent increases in postoperative complications and stomas, is to

be avoided. Interestingly, there are some early pioneer studies that have found potential advantages in the application of EN to malnourished patients, in whom they seem to produce better surgical results [20, 21].

Concerning therapy with CSTs, exclusive EN (EEN) has largely substituted prednisolone as first-line remission-inducing therapy for moderate to severe disease flares in children [22, 23]. In striking opposition, the former remain the mainstay of therapy for these situations in adults, in whom they seem more effective over EEN [24–26]. In this age group, the therapeutic value of EN in CD is controversial outside the bounds of malnutrition. It may therefore be advised as remission-inducing therapy in case of refusal or intolerance to CSTs, in mild extensive small bowel disease (here as primary or as adjuvant therapy), and as adjuvant therapy in the undernourished which maintain inflammatory stenosis, despite maximized adequate pharmacological therapy [24, 27–29]. The grade of evidence concerning the superiority of CSTs over EEN in adult patients is, however, of very low quality [24].

The mechanisms by which EEN induces remission of CD are not well established [29]. A number of studies suggest that EN promotes the balancing of mucosal cytokines – by decreasing those which are pro-inflammatory [30, 31], restores mucosal integrity and its barrier function [24, 30, 32], decreases adjacent mesenteric fat inflammation [33, 34], and alters the composition of the intestinal microbiome [35, 36]. It is possible that bowel rest and interruption of exposure to alimentary and some bacterial allergens may be contributing mechanisms [29].

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## Aim

To determine whether preoperative EN impacts postoperative complications of adult CD, either by means of nutritional or therapeutic effects.

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## Methods

A systematic review of research articles including the use of preoperative EN in adults with CD submitted to abdominal surgery, from January 1990 to November 2017, was conducted.

An initial search was carried out through PubMed-MEDLINE, ScienceDirect, and Google Scholar. Medical subject headings (MeSH) applied were the following:

- for PubMed-MEDLINE, “Crohn’s disease” AND “surgery” AND “postoperative” AND “complications” AND “adults” AND “preoperative” AND “enteral nutrition” AND “not review”; filters applied were “full text,” “English,” and “humans”;

- for ScienceDirect, “Crohn’s disease” and “enteral nutrition” (Title, abstract, keywords);
- for Google Scholar, “Crohn’s disease and preoperative enteral nutrition and adults.”

Two further searches were conducted:

- upon references of all articles selected as eligible, as result of the initial search;
- of “similar articles” of the two most recent studies of those already selected as eligible.

Methodology respected Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations [37].

Screening and testing for eligibility were performed upon English written abstracts. A grid was constructed to assess articles for eligibility and select them for inclusion, according to specific inclusion and exclusion criteria.

Inclusion criteria:

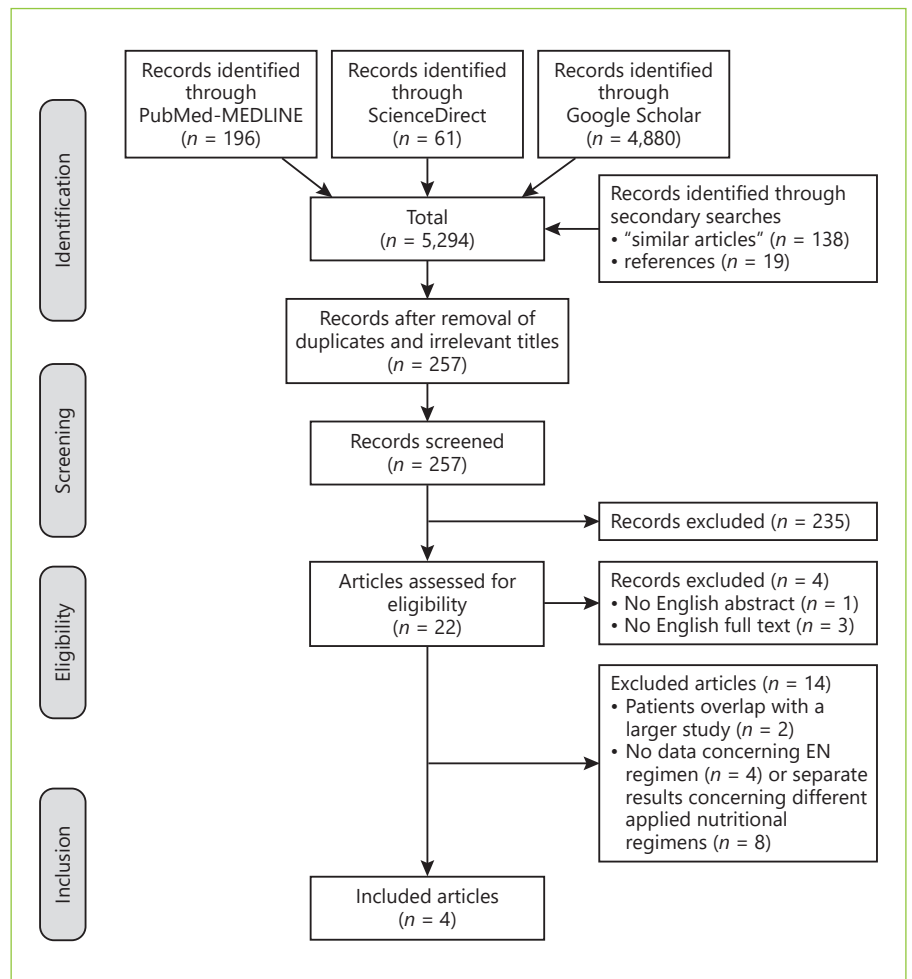
- Original clinical research articles wherein preoperative EN was administered to adult CD patients operated on for intestinal complications, as long as EN impact on postoperative complications is discriminated.
- English full-text articles published in peer-reviewed journals, including those published online ahead of print, within the time frame considered.
- Retrospective and prospective studies, whether cohort, case series, case control, or randomized controlled trials, regardless of aims and number of patients.
- Studies concerning adults – patients considered adults by the authors of the study were similarly assumed.
- All formulas, means of administration, and regimens of EN – exclusive or supplemental, as complement to PN or a conventional diet.
- Data referring to each type of nutritional regimen is accordingly discriminated and treated separately from that respecting patients and impact on postoperative morbidity.
- Paucity or even absence of data regarding repercussions of EN on patients’ preoperative state will not be criterion for exclusion.

Exclusion criteria:

- Review articles (both systematic and non-systematic), case reports, comments, letters, and book chapters.
- Abstracts of conferences, oral presentations, and posters presented in meetings.
- Papers concerning children or adolescents or whose authors belonged to pediatric institutions.
- Patient overlap among articles – the article containing the most patients was selected.
- Articles or results referring to the analysis of postoperative recurrence of CD.
- Absence of separate data concerning CD patients as opposed to those with ulcerative, undetermined, and unclassified colitis.

The quality of the studies was rated by awarding stars in each domain following the guidelines of the Newcastle-Ottawa Scale (NOS) [38].

Two authors (A.R. and I.B.) undertook the bibliographic search, independently screened the articles for eligibility, and assessed them thoroughly for inclusion. Discussion took place until consensus was reached whenever accordance was not met initially. Three authors (A.R., I.B., and P.L.) reviewed the included articles.



**Fig. 1.** Study selection process. EN, enteral nutrition.

## Results

One hundred and ninety-six references were identified in PubMed-MEDLINE, 61 in ScienceDirect, 4,880 in Google Scholar, and 157 through secondary search (Fig. 1). After the irrelevant titles and duplicates were removed, 257 records were screened, 22 of which were eligible. Of these, one had no English abstract [39] and three had no English full text [40–42]. The main features of the 14 full-text excluded articles are summarized in Table 1 [43–56] – eight of them had no separate results on different nutritional regimens or on treated patients [44, 47–50, 52–54] and four had no data on EN regimen [43, 45, 55, 56]; two other articles [46, 51] met the inclusion criteria but overlapped patients with a third study which contained a larger number of patients and was therefore detrimentally included. All studies in which supplemental EN was used with conventional diet or with PN did not meet the inclusion criteria.

The main characteristics of the four articles selected for review [57–60] are summarized in Tables 2–5. Table 2 refers to the general characteristics, aims, methods, indications for and information concerning preoperative EEN regimen, and main conclusions of the articles under review. Table 3 discriminates the characteristics of operated patient groups, the variables studied in each, studies' limitations, and the NOS quality assessment – criteria for which, as applied to cohort studies, being presented as online supplementary material (for all online suppl. material, see [www.karger.com/doi/10.1159/000494674](http://www.karger.com/doi/10.1159/000494674)) [38]. In Tables 4 and 5, the impact of preoperative EEN on clinical and surgical outcomes is detailed. No mortality was reported. Relevant data from these trials not expressed in the tables will be detailed below.

Li et al. [57] analyzed risk factors for postoperative complications after classifying 708 surgeries into four groups according to patients' preoperative management (Table 3). EEN was associated with a longer immunosup-

**Table 1.** Main features and criteria justifying exclusion of review candidate full-text articles

Authors, country and year of publication	Main cause of exclusion	Study design	Time frame	Aims	Total CD pts/ number of preoperative AN CD pts	Main results
Smedh et al. [43], Sweden, 2002	No data on EN formulation and on EEN-treated pts	Prospective	01-1996 to 01-2000	To find differences in post-op results between sutured and stapled anastomoses in CD intestinal resections	42 CD/21 EEN	Pre-op EEN, percutaneous drainage of abscesses, and weaning of CSTs, not the anastomotic technique, may have been decisive in the low post-op morbidity achieved
Zerbib et al. [44], France, 2010	Small number of EN-treated pts and no separate results on EN and TPN pts	Retropective	12-1997 to 01-2007	To evaluate the effect of pre-op treatment of sepsis and malnutrition and of drug withdrawal on post-op complications of penetrating CD	78 CD/5 EN, 45 TPN	In pts treated with pre-op AN, BMI $\leq 20$ and serum albumin $\leq 3.0$ mg/L were not risk factors for post-op complications; pts' pre-op management led to low post-op morbidity and a low stoma rate
Kanazawa et al. [45], Japan, 2012	No data on EN regimen and on treated pts	Retropective	01-2005 to 12-2010	To identify pre-op risk factors in CD pts for post-op IASCs	633 CD/325 EN	Penetrating CD, operating time $> 180$ min, and hand-sewn anastomosis were independent risk factors for IASCs
Li et al. [46], China, 2014*	Eligible for inclusion but pt overlap with a larger study	Retropective	02-2001 to 04-2011	To assess the effect of pre-op EEN on 3-month post-op IASCs in CD pts with enterocutaneous fistula	123 CD/55 EEN	Pre-op EEN and age $> 35$ years were independent protective factors against 3-month post-op IASCs
Zhu et al. [47], China, 2015*	No separate data or results on EEN-, PN+EN-, and TPN-treated pts	RCT	11-2011 to 12-2013	To assess whether the best pre-op AN goal is nutritional improvement or decreased CD activity	91 CD/78 EEN, 8 PN+EN, 5 TPN	Decrease in CD activity and nutritional improvement had similar surgical outcomes, but the first was achieved faster
Zhang et al. [48], China, 2015*	Limited data on EN regimen and no separate data on EN- and PN-treated pts	Retropective	04-2010 to 04-2014	To assess whether penetrating CD with or without intra-abdominal sepsis is a risk factor for post-op complications	288 CD/190 EN, 25 PN	Penetrating CD with abscesses was an independent risk factor for post-op complications; pre-op EN and serum albumin $> 3.5$ mg/L were protective factors
Zhang et al. [49], China, 2015	No separate data or results on EEN-, PN+EN-, and TPN-treated pts	Retropective	03-2008 to 05-2014	To evaluate the influence of pre-op BMI and serum albumin on IASCs in CD pts	64 CD/13 EEN, 15 PN+EN, 4 TPN	Pre-op BMI was a better nutritional indicator for IASCs than pre-op serum albumin
Guo et al. [50], China, 2016*	No separate data or results on EEN-, PN+EN-, and TPN-treated pts	Retropective	Not reported (paper accepted 08-2015)	To evaluate whether pre-op nutritional therapy in CD can reduce the risk of anastomotic dehiscence	123 CD/48 EEN, 6 PN+EN, 3 TPN	Pre-op nutritional support and serum albumin $> 3.5$ mg/L were independent protective factors against anastomotic leakage and primary stomata
Wang et al. [51], China, 2016*	Eligible for inclusion but pt overlap with a larger study	Retropective	01-2011 to 12-2012	To assess the value of pre-op EEN on post-op complications and CD recurrence rate	81 CD/42 EEN	Pre-op EEN for 4 weeks significantly increased serum albumin, prealbumin, and hemoglobin, improved pts' inflammatory status, and decreased infectious and non-infectious post-op complications
Guo et al. [52], China, 2017*	No separate data or results for pts treated with EN or PN followed by EN	Retropective	01-2013 to 01-2015	To assess risk factors for SSI in CD pts with gastrointestinal fistulae	118 CD/118 EN (29 $<$ and 89 $>$ 3 months), 79 PN followed by EN	Pre-op EN $<$ 3 months, anemia, and bacteria in fistula tract were independent risk factors for SSI; percutaneous abscess drainage was a protective factor
Dreznik et al. [53], Israel, 2017	No separate data or results on EN-, EN+PN-, and TPN-treated pts	Retropective	01-2008 to 12-2014	To evaluate if pre-op nutritional support in CD can reduce post-op complications	87 CD/14 EN, 17 TPN, 6 PN+EN	No difference found in 30-day post-op complications between two groups of pts – with and without pre-op nutritional support – but first group had a significantly lower readmission rate
Liu et al. [54], China, 2017*	No separate data or results on EN- and PN-treated pts	Retropective	01-2014 to 12-2016	To assess risk factors for post-op SSI after CD bowel resection with anastomosis	154 CD/141 EN, 104 PN $\pm$ EN	Low pre-op prealbumin, longer duration of surgery, and elevated intraoperative lactates were independent risk factors for SSI
Fumery et al. [55], France, 2017	No data on EN regimen or on EN- and PN-treated pts	Prospective nationwide	09-2010 to 08-2014	To assess frequency and risk factors for 30-day morbidity after ileocecal resection in CD pts	209 CD/32 EN, 30 PN	Four-week CST therapy was an independent risk factor for post-op complications
2015 ESCP Collaborating Group [56], 2017	No data on EN regimen or on EN- and PN-treated pts	International prospective snapshot audit	01-2015 to 03-2015	To evaluate pre- and intra-operative risk factors on 30-day post-op results after hemicolectomy and ileocecal resection for CD	375 CD/40 EN, 32 PN	Pre-op PN, surgery within 2 weeks, and unplanned intraoperative events were independent risk factors for post-op complications

CD, Crohn's disease; pt(s), patient(s); AN, artificial nutrition; EN, enteral nutrition; EEN, exclusive enteral nutrition; post-op, postoperative; pre-op, preoperative; CST, corticosteroid; TPN, total parenteral nutrition; BMI, body mass index; IASCs, intraabdominal septic complications; PN, parenteral nutrition; RCT, randomized controlled trial; SSI, surgical site infections; ESCP, European Society of Coloproctology. \* These papers were produced at the same Chinese institution as the one which produced the article by Li et al. [57] (Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, PR China), with collected data within overlapping periods of time (01-2001 to 03-2014).



**Table 2.** Characteristics, aims, methods, indications for and data regarding preoperative exclusive enteral nutrition, and main conclusions of the articles under review

Authors, country, and year of publication	Study design and time frame	Prospective data base	Aims	Inclusion criteria	Indications for pre-op EEN	EEN/ no-EEN patients, <i>n</i>	Type of EEN	Duration of EEN	Route of administration	Tolerance to EEN	Main results
Li et al. [57], China, 2015	Retro-spective cohort (01-2001 to 03-2014)	Yes	To evaluate the effect of pre-op EEN on 30-day post-op outcomes in CD pts	Abdominal surgery	Withdrawal of immunosuppression	219/561	Elemental*	Up to 8 weeks	NGT	Yes	Pre-op EEN was an independent protective factor against post-op infectious and non-infectious complications, significantly increased the drug-free interval, and decreased the emergent surgery, stoma, anastomotic leak, and reoperation rates
Heerasing et al. [58], UK, 2017	Retro-spective cohort (2008 to 2015)	No	To evaluate if pre-op EEN could provide a bridge to surgery to reduce post-op complications and CD recurrence rate	Strictureing and penetrating complications	Dietitian prescription	38/76	Polymeric TGF- $\beta$ 2 enriched <sup>†</sup>	6.3 weeks (mean)	PO	Yes	Pre-op EEN led to less inflammation and shorter operative time, protected against anastomotic leak and/or abscesses, and even avoided surgery in some pts
Beaupel et al. [59], France, 2017	Retro-spective cohort (06-2011 to 03-2015)	Yes	To assess whether EEN enriched with TGF- $\beta$ 2 could reduce 30-day post-op complications after surgery in high-risk <sup>§</sup> CD pts	Elective ileocecal or ileocolic resection	High-risk <sup>§</sup> pts	35 <sup>§</sup> /21	Polymeric TGF- $\beta$ 2 enriched <sup>†</sup>	21.6 days (median)	PO – 34 pts; NGT – 1 pt	All but 1 pt	No prognostic factors for post-op global and abdominal complications identified; TGF- $\beta$ 2-enriched EEN could limit the deleterious effects of high-risk factors for post-op complications
Zhu et al. [60], China, 2017	Retro-spective cohort (01-2011 to 06-2015)	No	To assess the value of EEN on 2-year surgery rate and on 30-day post-op morbidity in pts with percutaneously undrainable >1 cm intra-abdominal abscesses	Recurrent or not improving abscesses, and/or fistulae and/or bowel obstruction	Compliance/tolerance to EEN	46/28	Elemental*	39 days (median)	NGT	Yes	Pre-op EEN was an independent factor against surgery and significantly increased serum albumin, improved pts' inflammatory status, decreased IASCs, and led to a shorter post-op hospitalization

pre-op, preoperative; EEN, exclusive enteral nutrition; pt(s), patient(s); post-op, postoperative; CD, Crohn's disease; NGT, nasogastric tube; TGF- $\beta$ 2, transforming growth factor beta-2; PO, per os; IASCs, intraabdominal septic complications. \* Peptisorb Liquid® (Nutricia, Amsterdam, The Netherlands) – semi-elemental, 17.6 g carbohydrates, 1.7 g lipids, and 4 g protein/100 mL, 1 kcal/mL. <sup>†</sup> Modulen IBD® (Nestlé, Vevey, Switzerland) – polymeric TGF- $\beta$ 2 enriched, 54 g carbohydrates, 23 g lipids, and 18 g protein/100 mL, 1 kcal/mL. <sup>§</sup> High-risk patients: obstructive symptoms and/or penetrating CD and/or corticosteroid therapy and/or weight loss >10%.

pressant-free interval and fewer emergent surgeries, primary stomata, anastomotic leaks, intra-abdominal abscesses, wound infections, ileus, and reoperations on univariate analysis (Tables 4, 5). The authors identified EEN as an independent protective factor against postoperative complications (both infectious and non-infectious). Preoperative immunosuppressive therapy, perforation or abscess, emergent surgery, previous surgery for CD, and older age were independent risk factors for infectious complications (Table 5). The first two risk factors and longer operative time were the independent risk factors identified for non-infectious complications. The authors argued that the prospective nature of the database and the cohort nature of this study may have mitigated some of

the limitations and biases inherent to retrospective studies.

Heerasing et al. [58] retrospectively revised 51 patients treated with preoperative EEN after nutritional assessment. Thirteen patients (25%) ended up not requiring surgery. For each of the 38 operated EEN patients, two matched non-EEN controls were sought (Table 2). The latter were found to have higher basal body mass index (BMI), lower basal C-reactive protein (CRP) values and lower prevalence of treatment with antibiotics (Table 3). EEN was found to be an independent factor against anastomotic leaks and/or abscesses and led to significantly lower global postoperative morbidity and shorter operative times (Tables 4, 5). Patients with IASCs had signifi-

**Table 3.** Characteristics of operated patient groups, variables studied, and limitations of each reviewed article

Authors	Surgeries, <i>n</i>	EEN pts, <i>n</i>	No-EEN pts, <i>n</i>	Variables similar between study groups	Variables significantly different between groups	Study limitations	Newcastle-Ottawa score
Li et al. [57]	780	219 – group 4*	332 – group 1 <sup>†</sup> 29 – group 2 <sup>‡</sup> 128 – group 3 <sup>§</sup>	Pt gender and age at diagnosis and surgery, BMI, previous CD surgeries, disease duration, location and behavior, perforation/abscess, preoperative CSTs, immunomodulatory and anti-TNF treatment (compared with groups 2 <sup>‡</sup> and 3 <sup>§</sup> ), surgical indication, approach and main procedure, operative time, and blood loss; groups were not matched	Group 4* had > drug-free interval than groups 2 <sup>‡</sup> and 3 <sup>§</sup> , at surgery	Retrospective study; no sample size calculation; pts with digestive intolerance may be sicker than EEN pts	Poor quality
Heerasing et al. [58]	114	38	76 – straight to surgery	Pt ethnicity, gender, age, smoking status and comorbidities, previous surgeries, CD duration, Montreal classification, abscesses, weight, preoperative serum albumin, CSTs, immunomodulatory and anti-TNF treatment, and surgical indication and approach; groups were matched for age at diagnosis, disease duration and behavior, and type of surgery	EEN pts had < BMI and > baseline disease activity and CRP, and more often ATB at surgery	Retrospective data collection; small sample size; missing data on CD course and severity; incomplete matching of groups	Fair quality
Beaupel et al. [59]	56	35 high-risk <sup>  </sup>	21 low-risk – straight to surgery	Pt gender, age, smoking status, BMI, CD duration, perianal lesions and previous intestinal resection, serum albumin, immunomodulatory and biologic therapy, type of surgery and approach, anastomotic technique, and intraoperative findings; groups were not matched	High-risk EEN pts had > rate of obstructive symptoms and/or weight loss >10% and/or penetrating CD and/or CST therapy and > CD intractability	Retrospective study; small sample size; no control groups with different nutritional support; biased prescription	Poor quality
Zhu et al. [60]	74	46	28 – intolerant or noncompliant with EEN	Pt gender, HGB and WBC, previous surgeries, CD location and behavior, perianal lesions, CSTs, immunomodulatory and anti-TNF treatment at time of abscess diagnosis, abscess location, number of abscesses >3 cm, surgical approach, operative time, and intraoperative blood loss; groups were not matched	EEN pts had > serum albumin and < ESR and CRP at surgery	Retrospective study; small sample size; withdrawal of EEN before surgery in some pts and initiation of immunomodulatory or biological therapy after abscess resolution also before surgery, in others	Poor quality

EEN, exclusive enteral nutrition; pt(s), patient(s); BMI, body mass index; CD, Crohn's disease; CST, corticosteroid; >, higher; <, lower; CRP, C-reactive protein; ATB, antibiotic; HGB, hemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate. \* Group 4 – preoperative EEN and immunosuppressant-free interval (CSTs, immunomodulators, and biologics) less than 8 weeks. <sup>†</sup> Group 1 – without preoperative immunosuppressant therapy within 8 weeks of surgery. <sup>‡</sup> Group 2 – immunosuppressant therapy at surgery. <sup>§</sup> Group 3 – preoperative immunosuppressant-free interval less than 8 weeks. <sup>||</sup> High-risk patients: obstructive symptoms and/or penetrating CD and/or CST therapy and/or weight loss >10%. Criteria for application of the Newcastle-Ottawa Quality Assessment Scale to cohort studies are detailed in the supplementary material (Table 6).

**Table 4.** Impact of preoperative exclusive enteral nutrition on clinical outcomes and operative data

Authors; EEN/no-EEN patients, <i>n</i>	Medication withdrawal	Univariate analysis, <i>p</i>	Clinical impact	Univariate analysis, <i>p</i>	Impact on serum variables	Univariate analysis, <i>p</i>	Emergent surgery, %	Univariate analysis, <i>p</i>	Operative time, min	Univariate analysis, <i>p</i>
Li et al. [57]; 219*/332 <sup>†</sup> , 29 <sup>‡</sup> , 128 <sup>§</sup>	Group 4* had > drug-free interval than groups 2 <sup>‡</sup> and 3 <sup>§</sup>	<0.001	Group 4 had >↑ in BMI than groups 1 <sup>§</sup> and 3	0.003 <sup>§</sup> , 0.03 <sup>‡</sup>	N/A	–	Group 4 – 6.4 Group 2 – 51.7 Group 3 – 20.3	<0.001 <sup>‡</sup> , <0.05 <sup>§</sup>	Group 4 – 122 Group 1 – 132 Group 2 – 140 Group 3 – 129	ns
Heerasing et al. [58]; 38/76	No	–	No (weight and BMI)	ns	>↓ in CRP	0.02	N/R	–	EEN 3 h vs. no-EEN patients 3.5 h	<0.001
Beaupel et al. [59]; 35/21	CSTs – 62.5% of patients	–	No (weight loss >10%, BMI, and complicated CD)	ns	>↑ in albumin and >↓ in ESR and CRP	<0.05 and <0.001	N/A	–	N/R	–
Zhu et al. [60]; 46/28	N/R	–	N/R	–	>↑ in albumin and >↓ in CRP and ESR	<0.05/<0.001 and <0.001/<0.001 and <0.001	N/A	–	EEN 204 vs. no-EEN patients 198	ns

EEN, exclusive enteral nutrition; >, higher; ↑, increase; BMI, body mass index; N/A, not available; ↓, decrease; CRP, C-reactive protein; N/R, not reported; CST, corticosteroid; CD, Crohn's disease; <, lower; ESR, erythrocyte sedimentation rate. \* Group 4 – preoperative EEN and immunosuppressant-free interval (CSTs, immunomodulators, and biologics) less than 8 weeks. <sup>†</sup> Group 2 – immunosuppressant therapy at surgery. <sup>‡</sup> Group 3 – preoperative immunosuppressant-free interval less than 8 weeks. <sup>§</sup> Group 1 – preoperative immunosuppressant-free interval more than 8 weeks.

**Table 5.** Impact of preoperative exclusive enteral nutrition on surgical outcomes

Authors	EEN/no-EEN patients, <i>n</i>	Morbidity, %		Uni-variate analysis, <i>p</i>	Multivariate analysis	Anastomotic leak, %		Uni-variate analysis, <i>p</i>	Stoma rate, %		Uni-variate analysis, <i>p</i>
		EEN patients	no-EEN patients			EEN patients	no-EEN patients		EEN patients	no-EEN patients	
Li et al. [57]	219*/332†, 29‡, 128§	Infectious – 18.7*/non-infectious – 7.8*	Infectious – 51.7‡, 28.9†/non-infectious – 31†, 15.6‡	<0001/ <0.001	OR – 0.53 <sup>  </sup> / OR – 0.35 <sup>  </sup>	4.1*	17.2† 10.2‡ 3§	<0.05† <0.05‡ ns§	17.8*	65.5† 34.4‡ 22§	<0.001† <0.05‡ ns§
Heerasing et al. [58]	38/76	Global – 8/ anastomotic leak or abscesses – 3	Global – 32/ anastomotic leak or abscess – 20	<0.001/ 0.019	–/OR – 9.1**	N/R	N/R	–	3	8	ns
Beaupel et al. [59]	35/21	Global – 22.9/ ASCs – 14.3	Global – 23.8/ ASCs – 23.8	ns	–	2.8	0	ns	11.4	0	ns
Zhu et al. [60]	46/28	IASCs – 6.5	IASCs – 25	0.036	–	N/R	N/R	–	43.5	46.4	ns

EEN, exclusive enteral nutrition; OR, odds ratio; N/R, not reported; ASCs, abdominal septic complications; IASCs, intraabdominal septic complications. \* Group 1 – preoperative EEN and immunosuppressant-free interval (CSTs, immunomodulators, and biologics) less than 8 weeks. † Group 2 – immunosuppressant therapy at surgery. ‡ Group 3 – preoperative immunosuppressant-free interval less than 8 weeks. § Group 4 – preoperative immunosuppressant-free interval more than 8 weeks. || OR – likelihood of EEN patients having infectious and non-infectious complications, respectively. \*\* OR – likelihood of EEN patients not having anastomotic dehiscence or abscess.

cantly longer lengths of hospital stay and a higher readmission rate. The authors point out some limitations to this study such as missing data on medical records and incomplete matching of disease severity. Also, they did not clarify the reasons why control-matched patients did not receive nutritional support – it may even have been due to the baseline differences in BMI and/or serum CRP levels, but this was not mentioned.

Beaupel et al. [59] compared two groups of patients, 21 “low-risk” versus 35 “high-risk” for postoperative complications, distinct regarding CD behavior, severity and complications, nutritional state, and CST treatment (Tables 2, 3). As the rate of postoperative complications, for which no protective or risk factors were identified, was not statistically different between the two groups (Table 5), the authors admitted this indicated that TGF-β2-enriched EEN was beneficial for high-risk CD patients (Table 2).

In the study published by Zhu et al. [60], 54 of 83 CD patients were treated with EEN for abdominal abscesses not amenable to percutaneous drainage, either until abscess resolution or until surgery (from 7 to 1,000 days). The remaining 29 patients did not tolerate or comply with EEN and had a significantly higher cumulative 1-year surgical rate than EEN patients. EEN led to a higher rate of abscess resolution and was an independent protective factor against surgery. Previous abdominal surgery and abscess diameter >3 cm were independent risk factors for

surgery. Patients’ nutritional status was not mentioned. Forty-six EEN-treated and 28 EEN-untreated patients required surgery, the former having significantly fewer postoperative IASCs (Tables 2, 5). The authors noted limitations to the study beyond its retrospective nature and reduced number of patients: some of the latter suspended EEN and/or restarted immunosuppressants after abscess resolution, for unclarified periods of time.

In all studies, preoperative EEN was well tolerated by adults with complicated CD and a patent intestinal route – 338 out of 1,024 operated patients received preoperative EEN. Compared to their respective controls, patients under preoperative EEN achieved significantly lower levels of preoperative inflammatory markers in three of the reviewed studies [58–60], in two of which with concomitant increases in serum albumin values [59, 60]. The two studies with the greatest number of patients found preoperative EEN to be an independent factor against postoperative infectious and non-infectious complications [57] and against anastomotic leaks or abscesses [58].

However, quality grading for risk of bias according to NOS criteria [38] (Table 3) qualifies only one of the studies as “fair quality” [58] – the only one to match compared patient groups. The remaining studies were considered “poor quality,” essentially for not scoring in the comparability domain (see online suppl. material).



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## Discussion

All reviewed articles were institutional retrospective cohort studies with heterogeneous methods and inclusion criteria. Patients received preoperative EEN with different indications and regimens and for different periods of time. Those belonging to control groups were also heterogeneous between studies and even within the same study, namely regarding baseline nutritional state and CD activity, behavior, and medication. The type of postoperative complications analyzed also varied between studies. Meta-analysis was not done due to the small number of studies with varying designs, posing issues over the estimation of the between-study variance [61].

A non-intentional absence of studies referring to supplemental EN among those reviewed resulted from those which were eligible and referring to supplemental EN meeting exclusion criteria [44, 45, 47–50, 52–56].

From the reviewed articles, two were from China [57, 60], one of them being the study with the largest number of patients [57]. This latter study contains more patients than the sum of all three other reviewed papers, possibly raising transferability issues to other institutions and countries, namely, the Western ones. Although EN is not indicated as treatment for CD in adults by Chinese guidelines [62], eight of the excluded studies originated from China. The article by Li et al. [57] was produced by the same institution as that of seven [46–48, 50–52, 54] of the previous 8 studies, the latter being well known for its publications regarding this topic [31, 34, 63]. One of the excluded articles is Japanese [45]. The Japanese consensus indicates EN for remission induction and maintenance in adult CD [64] but, for the most part, studies from Japan focus on the possible impact of this nutrition on the reduction of postoperative relapse and remission maintenance – both as monotherapy and as an adjunct to pharmacotherapy [65–67].

Both reviewed Western studies made use of orally administered polymeric EEN [58, 59]. In both cases, an enriched formula with transforming growth factor beta-2 (TGF- $\beta$ 2) was used, the advantages of which have been studied for this pathology but not yet proved [17, 24, 68]. In the West, the administration of nutritional support by means of a nasogastric tube is poorly accepted by adults [24]. However, tolerance and acceptance towards the oral route has grown with improvements in the quality and variety of flavors of the polymeric formulations [24, 27].

In all studies, preoperative EEN was well tolerated by adults with complicated CD and a patent intestinal route, even in the presence of active inflammation and abdomi-

nal abscesses, leading to the possibility of postponing and even preventing surgery [58, 60]. A preoperative lag allowed for amelioration of patient conditions – reducing the inflammatory environment [58–60], increasing serum albumin [59, 60], weaning or suspending CST therapy [57, 59], and treating abscesses [59, 60] – as opposed to patients operated on immediately [58, 59]. These properties have also been attributed to nutritional support, both enteral and parenteral, by other authors [44, 47, 48, 50, 52–54, 69–72]. Also, in one of the reviewed studies [59], going straight to surgery (non-EEN patients) was an independent risk factor for anastomotic leaks and/or intra-abdominal abscesses.

The authors of one of the reviewed studies [60] refer that EEN led to a significant improvement in nutritional status based solely on a significant rise in serum albumin. Three articles specify BMI values [57–59], one of which also referring to weight loss above 10% [59] and another referring to basal and preoperative weights [58]. Nevertheless, in truth, none of the papers explains the methodology used for nutritional assessment. Standing alone, these anthropometric and laboratory parameters are not indicators of nutritional status in the presence of an active inflammatory syndrome, seeing they are highly influenced by variation in and retention of fluids [16, 49]. Preoperative serum albumin levels may reflect variations in a patient's inflammatory status and/or nutritional state and, therefore, for one or both reasons, values below 3 g/dL are a risk factor for postoperative complications in abdominal surgery [4, 5, 7, 11, 16]. The inflammatory environment elicited by the disease and surgery actively contributes to a descent in serum albumin and perioperative undernutrition, the control of the former being determinant in the improvement of the latter two [63, 73, 74]. In so being, nutritional support may be an essential weapon against the systemic inflammatory response syndrome and in promoting the restoration of the intestinal mucosal barrier, of immunological balance and tissue scarring, thereby leading to fewer postoperative complications and a faster recovery of the patient [16, 73, 74].

Two studies found preoperative EEN to be an independent factor against infectious and non-infectious complications [57] and against anastomotic leaks or abscesses [58]. However, only the study involving 780 surgeries [57] found EEN to lead to a significantly lower occurrence of postoperative emergent surgery, primary stomata, anastomotic leaks, and reoperations, as opposed to groups under immunosuppression alone. Although anastomotic dehiscence rates among the EEN and immunosuppressant-free groups were low (4.1 and 3%, respec-

tively), stoma rates were notably higher (17.8 and 22%, respectively) [57]. In the other three studies [58–60], stoma rates were similar between EEN and control groups but, in one of them, they were in fact very high (43.5 and 46.4%, respectively) [60].

It is noteworthy that no study reported on ostomies resulting from anastomotic dehiscence, on temporary ostomies that became permanent, or on ostomy closure morbidity. Yet, one of the main concerns of CD patients is that surgery may result in the need for an ostomy bag [75], which can lead to fear or even refusal of operations. Therefore, the possibility that preoperative EEN may lead to a lower stoma rate – whether primary or resulting from postoperative complications – is one of the most important aspects to consider in the surgery of these patients.

Despite the fact that all reviewed studies are retrospective and, consequently, of limited relevance, there is no doubt EEN was well tolerated and the preferred nutritional support, in the absence of intestinal obstruction, in the presence of complicated disease. In addition to its nutritional value, however, it is necessary to ascertain whether in fact this nutritional support conduces to mitigation of postoperative complications, reductions in stoma rates, decreased disease activity, removal of harmful drugs, and avoidance of emergent surgery.

The studies do collectively, nonetheless, call the attention of the scientific community to the potential benefits of preoperative EEN on postoperative outcomes in adult CD. They also carry enough impact to call for multi-institutional studies and randomized controlled trials. The design of this kind of trials, however, is a painstaking endeavor, since a great number of variables – relating to patients, disease, medication, surgical indications, and technique – must be considered. Also, ethical issues concerning randomization of malnourished CD patients towards receiving or not receiving nutritional support before surgery may limit the feasibility of such studies.

The determination of the properties of preoperative EEN is of importance since, as of now, this strategy has been very little or not at all used in most referral centers worldwide, outside the bounds of nutritional support.

Only then will the contribution of preoperative EN on postoperative morbidity and stoma rates of adult CD be defined.

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## Conclusions

In summary, preoperative EEN in adult CD surgery can be a valid option in specific situations – to improve nutritional status in the absence of intestinal obstruction, as an adjuvant to the treatment of existing abscesses and/or fistulas, and to attempt CST suspension.

However, none of the reviewed studies clarifies the possible existence of a cause-effect relationship between preoperative EEN and surgical morbidity in adult CD, their conclusions being far from definite. The few existing studies either carry obvious biases, varying risks of systematic errors, or questionable transferability of conclusions to other institutions. Prospective studies are required to establish whether or not preoperative EEN can in fact improve surgical outcomes in these patients.

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## Disclosure Statement

The authors declare no conflicts of interest.

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## Author Contributions

A. Rocha conceived and designed the study. A. Rocha and I. Bessa undertook the bibliographic research and, independently, screened the articles. A. Rocha, I. Bessa, and P. Lago selected for eligibility, determined inclusion, and reviewed the articles included. A. Rocha and I. Bessa drafted the manuscript. P. Lago, M.D. Santos, J. Leite, and F. Castro-Poças revised the draft and approved the final manuscript.

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