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INVITED REVIEW

Use of oral diet and nutrition support in management of stricturing and fistulizing Crohn's disease

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Abstract

Crohn's disease (CD), a form of inflammatory bowel disease, involves chronic inflammation within the gastrointestinal tract. Intestinal strictures and fistulas are common complications of CD with varying severity in their presentations. Modifications in oral diet or use of exclusive enteral nutrition (EEN) are common approaches to manage both stricturing and fistulizing disease, although supporting research evidence is generally limited. In the preoperative period, there is strong evidence that EEN can reduce surgical complications. Parenteral nutrition (PN) is often utilized in the management of enterocutaneous fistulas, given that oral diet and EEN may potentially increase output in proximal fistulas. This narrative review highlights the current practices and evidence for the roles of oral diet, EEN, and PN in treatment and management of stricturing and fistulizing CD.

KEYWORDS

Crohn's disease, digestive system fistula, enteral nutrition, inflammatory bowel disease, nutrition support, parenteral nutrition, stricture

INTRODUCTION

Crohn's disease (CD), a form of inflammatory bowel disease (IBD), involves persistent inflammation within the gastrointestinal tract. Manifestations may include inflammatory, stricturing (stenosing), and fistulizing (penetrating) disease. Each subtype of CD can present with mild, moderate, or severe disease, and a combination of clinical symptoms and endoscopic findings is used to determine severity. Clinical symptom severity is commonly measured in clinical trials using the Crohn's Disease Activity Index (CDAI), which consists of gastrointestinal symptoms, extraintestinal manifestations, weight change, abdominal mass on examination, and anemia. Scores are categorized as remission, <150; mild to moderate disease, 150–220; moderate to severe disease, 220–450; and severe disease, >450.[1] Current targets in therapy of CD include both symptomatic and endoscopic remission.

Strictures consist of narrowing within the gastrointestinal tract and are a well-known complication of long-standing CD (Table 1), with 25% of patients with CD having at least one small bowel stricture and 10% having at least one colonic stricture.[4] An estimated 20% of strictures in CD are asymptomatic and unlikely to require surgery.[5] Symptoms of stricturing disease range from mild abdominal cramping and/or bloating to severe abdominal pain, nausea, vomiting, and obstipation that require hospitalization. The most common clinical and environmental risk factors for the development of

TABLE 1 Phenotypes of stricturing and fistulizing disease in Crohn's disease.[2,3]

Phenotype	Description
Stricturing disease	
Fibrostenotic stricture	A narrowing of the bowel lumen due to accumulation of scar tissue induced by inflammation
Fistulizing disease	
Entero-enteric fistula	An abnormal connection between the two areas of the small bowel
Enterocolic fistula	An abnormal connection between the small bowel and the colon
Enterocutaneous fistula	An abnormal connection between the small bowel and the stomach or the skin
Enterovesical fistula	An abnormal connection between the small bowel or colon and the bladder
Enterovaginal fistula	An abnormal connection between the small bowel, colon, or rectum and the vagina
Perianal/perirectal fistula	An abnormal connection between the rectum or anus and anal or perianal tissue

stricturing disease include age of diagnosis <40 years, perianal disease, need for steroids during initial CD flare, and smoking history.[2] Luminal narrowing may arise from active inflammation or long-standing fibrosis, although most strictures possess varying degrees of both inflammation and fibrosis. Anti-inflammatory medications (steroids, immunomodulators, biologic therapies) can help reduce inflammatory strictures, but there are currently no antifibrotic medications yet available for fibrotic strictures.[6] Endoscopic options (eg, balloon dilation, strictureplasty) and surgical options (eg, strictureplasty, bowel resection) otherwise exist for medication-refractory strictures.[7]

Fistulas within the gastrointestinal tract are abnormal connections between the gastrointestinal tract and a nearby organ or skin. The cumulative risk of fistula formation in CD is 33% after 10 years of diagnosis and nearly 50% after 20 years.[3] Age of diagnosis <40 years and prior history of stricturing disease are identified risk factors for development of fistulizing disease.[8] Symptoms may vary depending on the type and location of the fistula, although commonly abdominal pain and diarrhea are present. Perianal fistulas are most common, although entero-enteric, enterocolic, rectovaginal, enterocutaneous, and enterovesical fistulas can also be seen (Table 1).[3] For fistulizing disease, anti–tumor necrosis factor (anti-TNF) therapies are effective for closure of perianal fistulas, whereas data remain limited on other biologic therapies for intestinal fistulas.[9] Even for perianal fistulas, most data suggest long-term remission rates are poor.[10] Despite anti-TNF therapies, surgical trends demonstrate significant increase in the rates of surgical repair of small bowel fistulas, suggesting biologic treatment may not necessarily prevent requirement for surgery.[11]

Besides medical and surgical treatments, a critical facet in the management of stricturing and fistulizing CD is nutrition therapy. This narrative review discusses current evidence and practices of oral diet, exclusive enteral nutrition (EEN), and parenteral nutrition (PN) in stricturing and fistulizing CD, as well as perioperative considerations for nutrition for these CD phenotypes.

METHODS

To identify the relevant literature for this topical review, we performed a query of articles catalogued in PubMed from inception through December 12, 2022. The search terms included the following: "(Inflammatory bowel* or IBD or Crohn* or ileitis or enteritis or enterocolitis) AND (obstruct* or strict* or stenos* or fibros* or fistul* or penetrating) AND (diet* or food* or nutr* or feed* or fibr* or fiber or veget* or fruit or grain* or eliminat* or element*)". After article de-duplication, there were 6284 articles for title and abstract screening by at least one author, thereafter yielding 415 relevant articles. Inclusion criteria included all article types that discussed nutrition in the context of CD in humans. Unpublished studies presented at national conferences were added when deemed relevant by any of the authors. Exclusion criteria included in vitro or animal studies whose findings were deemed too remote for clinical application. Redundant articles and articles in languages other than English were not automatically excluded. The body of relevant articles was then used where appropriate for the development of this narrative review.

ORAL DIET

Diet has been proposed to play a role in the development of IBD. In CD, a diet pattern with low fruit and vegetable intake and high intake of processed foods (snacks, prepared meals, nonalcoholic beverages, sauces) was associated with increased risk, although data are limited

for diet patterns associated with stricturing and fistulizing disease.[12] Additionally, certain food additives have been associated with CD; however, there is a paucity of data focusing on stricturing and fistulizing disease.[13–16] Given diet's role in development of IBD, various diets have also been investigated as treatments for CD. Multiple studies have evaluated various exclusion diets in treatment of CD, such as the specific carbohydrate diet (SCD) and the Crohn's Disease Exclusion Diet (CDED). The SCD was initially developed in the 1920s and involves eliminating complex carbohydrates and refined sugars that may be malabsorbed and subsequently promote bacterial dysbiosis that can aggravate intestinal inflammation.[17] The CDED refers to a three-phase dietary plan in which proinflammatory foods that may negatively alter the microbiome and intestinal epithelium are avoided to improve CD symptoms.[18] The studies involving these diets have shown variable efficacy in achieving clinical and biochemical remission in patients without stricturing and fistulizing disease.[18,19] In CD, a randomized controlled trial of 194 adult patients with CD without stricturing or fistulizing disease found there were no significant differences in rates for symptomatic remission or reduction in C-reactive protein (CRP) and fecal calprotectin levels between adherence to the Mediterranean diet and adherence to the SCD.[20] Studies evaluating the use of any of these diets in patients to reduce strictures and fistulas are minimal. Supplementation with probiotics to oral diet has demonstrated no utility in remission of CD as well.[21]

Stricturing disease

Anti-inflammatory dietary effects could theoretically benefit patients with inflammatory strictures; however, there are currently no data to suggest diet's anti-inflammatory properties significantly alter clinical outcomes in the setting of an acute inflammation-mediated obstruction. For mechanical intestinal obstruction, a diet with modified consistency could be useful for inflammatory and fibrotic strictures.[22] Traditionally, patients are asked to modify consistency and limit intake of insoluble fiber to reduce risk of obstruction, although this practice has limited supporting evidence. Earlier case series from the 1950s determined that certain foods (orange, watercress, and almonds) along with inadequate chewing may contribute to development of obstructions.[23] From the authors' experience, modified consistency of fiber has been well tolerated overall in those with stricturing disease and can certainly continue as tolerated (Table 2). Tolerance to intake of types of fibers may vary from patient to patient, and therefore, fiber intake along with its modified consistency should be individualized to reduce risk of unnecessary food restrictions. Further studies are warranted in the use of diets and modified consistency in management of stricturing disease.

Fistulizing disease

Studies for use of diet in management of most presentations of fistulizing disease are limited.

Diet intake has been often restricted or eliminated in patients with a high-output enterocutaneous fistula (>500 ml/day) to reduce output and promote closure of the fistula (in conjunction with immunosuppressive therapies).[24] Nutrition management for enterocutaneous fistulas may include a high-calorie, high-protein, high-sodium diet with inclusion of oral rehydration solutions to support absorption of sodium and water.[24] Diet may need to be supplemented with oral nutrition supplements to provide additional calories and protein as needed.

EXCLUSIVE ENTERAL NUTRITION

Several meta-analyses have demonstrated the efficacy of EEN for the induction of remission in CD.[25–27] EEN, an established modality for nutrition in IBD, is defined as providing 100% of a person's nutrition requirements through a liquid nutrition formula (polymeric, semielemental, or elemental) delivered by a feeding tube or orally.[28] Beyond EEN, we further define partial enteral nutrition (PEN) as the use of liquid formula by either tube feeds or oral route with incorporation of solid foods as well. The term “enteral nutrition (EN)” in our review refers to both EEN and PEN. Based on prior evidence, the European Crohn's and Colitis Organisation (ECCO) and European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) consensus guidelines currently recommend EEN as first-line therapy to induce remission of active luminal disease in pediatric populations with CD.[29] However, these guidelines note that stricturing and penetrating disease are more likely to require anti-TNF therapy, owing to increased risk of poor disease outcome. A 2006 randomized controlled trial that compared adult patients with CD who received PEN vs those who consumed their regular diet found a significantly lower relapse rate in the PEN group.[30]

There are several potential mechanisms by which EEN is thought to improve outcomes in CD (Figure 1). The first is through anti-inflammatory effects.[31] EEN has been shown to decrease proinflammatory cytokine production, specifically interleukin (IL)-6 and IL-8, in mouse models.[32] Whole foods may also have antigens

TABLE 2 Oral diet for stricturing disease in Crohn's disease.[a]

Eat	Limit
Meat, poultry, fish:	
Any tender cut; also may need to consider ground, shredded, blended forms	Tough cuts that are difficult to chew
Dairy:	
Any; also may need to consider lactose-free/low-lactose forms or dairy substitutes (eg, almond, rice, oat milk) if dairy is not tolerated	
Breads, pastas:	
Breads (English muffin, sourdough), cereals (eg, cornflakes, cream of wheat/rice, oatmeal), graham/saltine crackers, noodles, pancakes, pastas, white rice, tortilla, waffles	Multigrain breads, granola, popcorn, brown/wild rice
Fruits/vegetables:	
Watermelon; applesauce; avocado; banana; canned fruits; peeled fruits/vegetables (any); well-cooked vegetables (eg, carrots, spinach, zucchini); polenta; sweet potato; mashed potato; any fruit or vegetable puree, sauce, or smoothie	Fruit/vegetable skins; whole forms: orange, grapefruit, dried fruit, fig, prunes, broccoli/cauliflower, corn on the cob, alfalfa sprouts, asparagus, brussels sprouts, cabbage, celery, mushroom, okra
Legumes:	
Creamy nut butters, soft tofu, blended beans/lentils, hummus	Whole forms: beans, black-eyed peas, lentils, nuts, crunchy nut butters, edamame
Beverages:	
Water, coffee, tea	Prune juice
Seasonings, condiments:	
Broth, butter, honey, jelly, gravy, maple syrup, mayonnaise, mustard, olive/avocado oils, pesto, salad dressings, vinegar, salt/pepper/sugar	Coconut, olives, pickles, all seeds (eg, chia, pumpkin, sunflower)

Notes: Diet must be individualized, as tolerance can vary from patient to patient. Modified consistency (eg, blended, mashed, minced, chopped, peeled) can be considered for those who are having difficulty tolerating whole forms of fiber. Diet must be evaluated on an ongoing basis to adjust diet in conjunction with medical treatment. Include sips of fluids with all meals. All foods must be chewed well.

[a]Dietary recommendations based on authors' expert opinion.

that could promote intestinal inflammation, compared with elemental or nonelemental formulas.[31,33] EEN may improve outcomes via modification of proinflammatory microbiota. Several studies have demonstrated changes in gut microbiota, with association of microbiota changes similar to those with remission from CD.[34–36] EEN may also induce mucosal and transmural healing and reverse gut permeability seen in CD, which may further improve outcomes.[31,37]

Stricturing disease

The current literature surrounding the efficacy of EEN in stricturing disease is primarily limited to case reports and single-center observational studies. The earliest reports of the potential benefits of EEN come from a 1990 longitudinal study of 113 adult patients from 1977 to 1988 who received a defined course of an exclusive elemental diet (for up to 12 weeks) as treatment for CD.

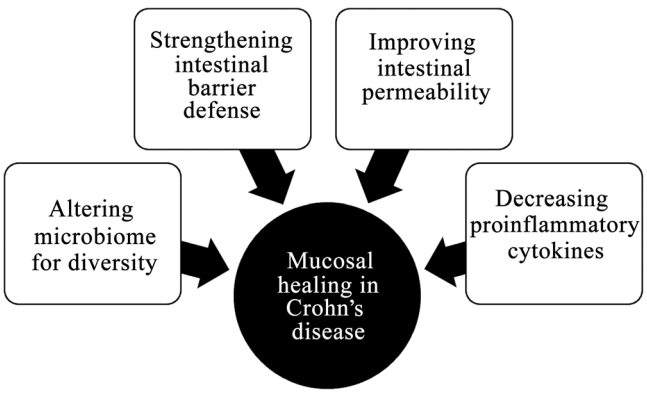

FIGURE 1 Proposed mechanisms for exclusive enteral nutrition in Crohn's disease.

The diet was delivered through oral intake or nasogastric tube if unable to tolerate oral intake. Of the 113 patients, 35 of the patients had symptomatic strictures and 33 (94%) were able to achieve remission after treatment,

although 12 did undergo elective surgery in the remission period.[38]

Several retrospective and prospective studies further expanded on the role of EEN in stricturing disease, with many of these studies coming from Chinese patient populations. A 2010 Chinese study demonstrated that in 37 patients with incomplete intestinal obstruction, a 12-week EEN treatment course by feeding tube was associated with significantly decreased CDAI at 4 and 12 weeks, with 78% of patients developing clinical remission.[39] Seven cases required surgery. Another study identified 41 adult patients with complicated CD who received a 12-week course of EEN. Of the 10 patients with strictures, 2 (20%) had no response to EEN and required surgery, 2 (20%) had partial remission, and 6 (60%) achieved complete clinical remission.[40] The largest study specifically looking at patients with stricturing disease was a 2014 Chinese study in which 59 adult patients with evidence of active inflammatory stricture were treated with 12 weeks of elemental EEN, with 73.8% of patients achieving symptomatic remission, 53.8% achieving radiologic remission, and 64.6% achieving clinical remission.[41] In this study, there was also a significant improvement in inflammatory markers (CRP, erythrocyte sedimentation rate [ESR]), acute phase reactants (albumin, prealbumin), and body mass index (BMI; defined as weight [kg] divided by square height [m^2]) at 4 and 12 weeks.

In a retrospective 2016 Korean study, pediatric patients with CD underwent a 6-week induction course of oral EEN with an elemental formula and then tapered off to a course of PEN over several months.[42] Of the seven patients with stricturing disease, four (57.1%) were able achieve clinical improvement; of those four, three were able to have extended symptomatic improvement during the maintenance period. Another retrospective study from India identified outcomes of adult patients with complicated CD who received EEN. Patients received either semielemental or polymeric formula (based on availability and patient preference). Patients were included who used EEN as the exclusive treatment modality or in combination with other therapies (steroids, immunomodulators, and/or anti-TNFs). Of 18 patients having a stricturing phenotype, 78.8% experienced a clinical response (defined by a CDAI reduction of >70).[43]

These outlined studies have demonstrated the potential for EEN or PEN as a therapy in the setting of stricturing CD, but a significant need remains for additional research on the subject, given the small sample sizes and substantial heterogeneity across studies. The studies also lack a control group or comparison with other treatment modalities, limiting the conclusions that can be made about the efficacy of EEN.

Fistulizing disease

Early case reports outline the potential benefits of EEN in the management of fistulizing CD. A 2008 case report from the pediatric literature describes a patient with an enterovesical fistula treated initially with PN, antibiotics, and immunosuppressive medications with eventual transition to EEN with a polymeric formula (with eventual transition to PEN and slow wean off formula) and eventual clinical remission at 18 months.[44] It is unclear from the report whether this patient received EEN by a feeding tube or oral approach. This case highlights the potential benefits of EEN in treatment of fistulizing CD, but it is difficult to ascertain its effect, given the multiple therapies offered in treatment of this patient.

Another pediatric case series describes the use of EEN in the management of perianal fistulas.[45] The case series describes two adolescent boys, both diagnosed with ileocolonic CD with perianal fistula and abscess, requiring incision and drainage. In both cases, patients initiated EEN with a polymeric formula for 8 weeks. The EEN protocol in these patients was a trial of oral route with nasogastric tube feeding if unable to tolerate oral feeding, although it appears both patients tolerated the oral route. One patient demonstrated improvement in his CDAI score after 4 weeks with prolonged remission, whereas the other only achieved biochemical remission. In these studies, we see EEN may play a primary role in treatment of fistulizing perianal disease.

Sood et al. assessed peptide-based EEN as a treatment option in Indian adult patients who were refractory to anti-TNF therapy.[46] Six patients were identified with moderate to severe CD, two of whom had perianal fistulas and two of whom had entero-enteric fistulas. Both patients with perianal fistulas had undergone seton placement initially. Patients in the perianal subset demonstrated decreased drainage by 50% by 12 weeks, although they did not achieve healing. The patients with entero-enteric fistula demonstrated complete healing on magnetic resonance enterography at 12 weeks.

There has additionally been research into the efficacy of EEN in the setting of abdominal enterocutaneous fistulas with CD. A 2014 prospective study identified 48 adult patients, 8 of whom were determined to have spontaneous fistulas and 40 with postoperative fistulas, who were all treated with continuous peptide-based EEN through nasogastric feeding for 3 months.[47] Thirty of the

40 patients (75%) had successful closure by 3 months, with significant improvement in inflammatory markers, including platelets, ESR, and CRP. Markers of nutrition status such as body weight and BMI also improved. Eight patients relapsed and required bowel resection surgery. Given that 40 of these patients had fistulizing disease after surgeries, it is difficult to ascertain whether the etiology of these fistulas was inflammatory in nature and whether the potential anti-inflammatory effects of EEN played a role in their resolution. Additionally, post-operative enterocutaneous fistulas have higher closure rates than spontaneous fistulas secondary to active CD.[48]

Several studies previously mentioned in the review of EEN for stricturing disease also included patients with fistulizing disease. A UK study with 10 years' experience of adult patients with CD receiving EEN with elemental formula showed that 8 of 10 patients with intestinal fistulas achieved complete healing of their fistulas, although the locations of these fistulas were not available.[38] In a study by Chen et al., in which patients were treated with specifically oral EEN and azathioprine, all 7 patients with fistulas (of 29 patients total in the study) had fully healed fistulas by 1 year.[37] Another study assessing EEN in complicated CD from Yang et al. demonstrated that of 33 patients with fistulizing disease, 27 achieved clinical remission after 12 weeks of EEN.[40]

One special consideration for nutrition support is the use of fistuloclysis in the setting of entero-atmospheric fistulas. Entero-atmospheric fistulas are abnormal connections between the small bowel and skin from a prior skin wound and result in visible bowel lumen in the wound, with separation of the abdominal wall fascia. They are often secondary to a ventral hernia or prior surgery. Traditionally, PN was the nutrition modality used for entero-atmospheric fistulas; however, fistuloclysis, in which a feeding tube is inserted into the distal limb of the fistula and nutrition is provided by the enteral route, has become a potential alternative.[49] This technique is relatively rare in the US population, however.[50] Entero-atmospheric fistulas secondary to CD are very rare, and there are no retrospective, prospective, or randomized controlled trials demonstrating efficacy for fistuloclysis in CD; however, there are few case reports and case series that describe this nutrition approach.[51,52] A significant concern with fistuloclysis is the potential for obstruction distal to the site of tube feeds, either from adhesions or other sites of distal stricturing CD.

The existing literature suggests potential benefit for EEN or PEN in the setting of fistulizing CD, but the literature, much like for stricturing disease, remains limited to case reports and observational studies without comparison arms. For both stricturing and fistulizing disease, the sparse sample of studies suggests potential for publication bias. Given some of the heterogeneity seen in outcomes among different types of fistulas as well, further research is needed to determine whether there are particular locations for fistulas that may respond better to EEN and why. In addition to location of the fistula influencing outcomes, the variability in EEN formulations, such as polymeric or elemental, may influence outcomes, but existing literature is not robust enough to determine optimal formulation.

PARENTERAL NUTRITION

PN has been traditionally used to provide nutrition to patients who are severely malnourished or who have been placed on bowel rest during active disease. The rationale of bowel rest is to reduce interactions between dietary antigens and the diseased bowel while providing nutrients to support nutrition status. Nonetheless, this practice has limited evidence. The use of PN and bowel rest in an early randomized study of 47 adult patients with severe acute colitis (CD and ulcerative colitis [UC]) on intravenous prednisolone showed a decrease in daily frequency of bowel movements. The bowel rest among the patients with CD also led to less surgery in comparison with the patients with UC (0 of 16 vs 14 of 27).[53] Information regarding stricturing or fistulizing disease was not provided by the authors of the aforementioned study. A later study of 51 adult patients with active CD showed no differences in 1-year remission rates between patients receiving PN and bowel rest, tube feeding, or partial PN with unlimited diet.[54]

Stricturing disease

PN is indicated for strictures and/or their consequent bowel obstructions when diet is contraindicated and use of EN is not feasible beyond the site of obstruction.[22]

There are limited studies of the use of PN in stricturing disease. An early retrospective study evaluated use of PN in 100 hospitalized patients with CD, in which 29 patients had a subacute obstruction.[55] The PN was provided to patients as three different formulations, with the first formulation providing a mixture of 50% dextrose and 50% lipids, the second formulation contributing 83% as lipids with provision of protein at 1 g/kg/day (based on kilograms of ideal body weight) along with a caloric target (nonprotein) at 40 kcal/kg, and the third formulation being given solely with protein at 1.7 g/kg/day. The average duration of PN use was 25 days. Medications, including sulfasalazine, azathioprine, antidiarrheal agents, and analgesics with the exception of steroids, were stopped prior to PN initiation. The primary outcome measured was no recurrence of symptoms of obstruction

once diet was introduced or a CDAI score <150. Results showed that 76% of the patients with the obstruction achieved clinical remission and maintained remission at the 3-month follow-up visit.

Fistulizing disease

Oral diet and/or EEN can likely be utilized in patients who have a distal fistula (ileal or colonic), but PN will likely serve as the primary source of nutrition for patients who have more proximal or high-output enterocutaneous fistulas and are experiencing malnutrition, fluid, and electrolyte abnormalities.[22,24] The presence of a proximal enterocutaneous fistula may require patients to be completely dependent on PN, owing to decreased effective bowel length for digestion and absorption of oral nutrients and fluids.[56] With oral diet or EEN contributing to an increase in the volume of an enterocutaneous fistula, PN initiation should commence as soon as possible.[56] In addition to meeting caloric, macronutrient, and micronutrient needs, the prescription for the PN regimen should factor in the volume of losses from the enterocutaneous fistula to aid in fluid and electrolyte replenishment.

Data surrounding the use of PN for fistulizing disease are very sparse and limited to a singular, low-quality case report. An adult woman with prior diagnosis of UC with prior ileal pouch–anal anastomosis surgery developed new abscess and enterocutaneous small bowel fistula concerning for CD.[57] PN was initially started with subsequent addition of tube feeds with semielemental formula. PN was discontinued after 4 weeks, and after 6 weeks of EEN, the patient transitioned to an oral diet with spontaneous closure of the fistula and resolution of abscess. Of note, this patient's presentation may have been a result of surgical complications, and the diagnosis of CD was not confirmed.

PERIOPERATIVE NUTRITION CONSIDERATIONS FOR SURGERY

For both stricturing and fistulizing disease, need for surgery is common, with prior studies reporting 50% of patients with stricturing CD and 80% of patients with fistulizing CD will require surgery,[3,58] In the interest of bowel preservation, patients with stricturing disease who are asymptomatic are not typically recommended to undergo surgery unless there is an overlapping medication-refractory inflammatory or fistulizing phenotype present. The presentation for urgent surgery to address a complete small bowel obstruction is less common and may be seen in patients who lack specialty care to diagnose and manage CD or in patients who have been unable to adhere to medical management. Although fistulizing disease can be well controlled with immunosuppressive therapy, certain types of fistulas, such as enterocutaneous, enterovaginal, or enterovesical fistulas, may continue to result in bothersome symptoms related to pain and localized infections requiring surgical resection.

Malnutrition is a risk factor for postoperative complications.[59] Early administration of EEN and PN should be considered at least 7 days prior to surgery in patients with malnutrition undergoing surgery if diet is anticipated to be met with poor tolerance or not consumed in sufficient amounts to meet >50% of estimated nutrition needs. Although EEN or PEN is generally preferred over PN for nutrition support in the preoperative period when the gastrointestinal tract is functional, there are cases in which EEN or PEN are contraindicated and PN must be used (Table 3).[60,61]

One specific consideration for preoperative nutrition involves the rare patient with CD who has a temporary double enterostomy in the proximal-to-mid small intestine. Traditionally, PN is used for nutrition until surgery can restore the intestinal continuity, but few recent studies have demonstrated patients with temporary double enterostomies, including those with CD, can be provided nutrition through chyme reinfusion through the distal portion of the intestine.[62,63]

PREOPERATIVE EN

The most widely studied perioperative nutrition intervention in CD is preoperative EN, with most studies being retrospective or retrospective analyses of prospective series focusing on the primary end point of postoperative complications (Table 4). The existing literature generally combines stricturing and fistulizing disease, but most studies do not perform subgroup analysis of outcomes in those with stricturing disease, limiting our ability to draw conclusions for this subpopulation. Few studies focus on postoperative nutrition needs or support.

The optimal length of timing and level of dependence for preoperative EN in both fistulizing and stricturing CD remain unclear. Studies have reported varying time intervals for preoperative EEN, but most required at least 2 weeks. Heerasing et al. considered EEN adequate if it was administered to patients for at least 2 weeks.[64] Abdalla et al. considered 1 week of EEN delivered to patients to be sufficient.[65] Studies out of Asia tend to use a longer duration of EEN, possibly related to the tendency for these patients to be managed in the inpatient setting, where a nasogastric tube can be used and adherence may be more easily encouraged, with several studies from China providing EEN to patients for

TABLE 3 Indications and contraindications for oral diet and nutrition support in stricturing and fistulizing disease in Crohn's disease.

	Indications	Contraindications
Stricturing disease		
Oral diet[22,23]	– Modified-consistency oral diets may be used as first line for nutrition if patient can safely tolerate	– Significant bowel obstruction
Exclusive enteral nutrition[38–43]	– May have benefit as adjunct therapy in induction and therapy, particularly in pediatric populations	– Significant bowel obstruction
Parenteral nutrition[22]	– Inability to tolerate oral or enteral nutrition due to significant bowel obstruction	– Active catheter-associated thrombosis – Bloodstream infection or catheter-associated infection
Fistulizing disease		
Oral diet[24]	– Distal fistula (ileal or colonic)	– High-volume enterocutaneous fistula – Proximal fistula
Exclusive enteral nutrition[37,38,40,44–47]	– Distal fistula (ileal or colonic)	– High-volume enterocutaneous fistula – Proximal fistula
Parenteral nutrition[22,24,57]	– Inability to tolerate oral or enteral nutrition – Presence of enterocutaneous fistula worsened by enteral or oral nutrition	– Active catheter-associated thrombosis – Bloodstream infection or catheter-associated infection

TABLE 4 Perioperative considerations for EEN and PN for stricturing and fistulizing disease.

	Considerations
Stricturing disease	
EEN[64–68]	– Consider EEN as first line for nutrition preoperatively, regardless of nutrition status. – A 2-week course of EEN may be beneficial to reduce postoperative complications for those undergoing surgery for stricturing disease.
PN[69–71]	– Consider PN in patients for whom EEN may be unsafe because of severity of strictures and concurrent severe malnutrition.
Fistulizing disease	
EEN[64,65,68,72]	– EEN may provide benefit in reducing postoperative complications; however, there is some signal that patients with fistulizing disease may have increased risk of postoperative infections and need for PN.
PN[73]	– PN is a feasible option for nutrition in the preoperative period for those unable to take EN, but there is limited evidence for efficacy or safety.

Abbreviations: EEN, exclusive EN; EN, enteral nutrition; PN, parenteral nutrition.

at least 4 weeks.[66,67,74] Another small study from Japan provided EEN to patients for 2–4 weeks preoperatively.[75]

Stricturing disease

In a widely cited study from the United Kingdom, Heerasing et al. used a case-control methodology to compare 38 adult patients who received 2 weeks of polymeric EEN via oral route with 76 controls matched on age, disease duration, disease type, and surgical procedure.[64] Stricturing disease constituted nearly half of the cases—47% in both the group receiving EEN and the control group. The mean duration of EEN was 6.3 weeks. Rates of anastomotic leak, postoperative abscess, or fluid collection were significantly lower in the patients receiving EEN (3%) vs controls (20%).

Meade et al. sought to examine the impact of EEN on postoperative complications in a retrospective cohort using intention-to-treat and per-protocol approaches, depending on adherence to EEN.[68] They reviewed 204 adult patients receiving EEN via oral route and compared them with a "nonoptimized cohort" of 96 patients who

did not have any nutrition support preoperatively. The study by Meade et al. was relatively large and favored preoperative EEN, but the proportion of patients with stricturing disease was not specifically reported. Instead, prestenotic dilation ≥3 cm was reported. Prestenotic dilation was seen in 47% of the per-protocol group and 39% of the nonoptimized group, suggesting that this study could apply to patients with a stricturing disease. Patients had polymeric or elemental EEN for at least 2 weeks at 600 kcal/day or more. Patients who had PEN were those who did not or could not take the full volume and were thus supplemented with normal diet. Multivariable analysis in the per-protocol group showed fewer wound infections and lower readmission rates. There was a trend toward lower surgical complications in the patients in the per-protocol group receiving EEN. The larger intention-to-treat group included 30% who could not adhere to the EEN parameters, but these patients were noted to have statistically significant lower rates of complications compared with the nonoptimized group.

Yamamoto et al. recently reported a small study comparing 24 adult patients who had 2–4 weeks of elemental EEN, via oral or nasogastric tube feed, vs 24 patients who had neither EEN nor PN.[76] Stricturing phenotype comprised 11 (46%) patients in each group. Septic complications (anastomotic leak, intra-abdominal abscess, enterocutaneous fistula, or wound infection) were significantly less frequent in the patients receiving EEN compared with the control group (4% vs 25%).

Abdalla et al. performed a secondary analysis on the GETAID trial data on anti-TNF therapy and postoperative morbidity.[65] One hundred forty-nine adults were selected from this prospective multicentric cohort of patients undergoing elective surgery for ileocolic CD. Unlike most of the studies evaluating preoperative EEN, this study focused on malnourished patients, defined by BMI <18 and/or albuminemia <30 g/L and/or weight loss >10% from baseline. Nearly half of these patients had stricturing disease. EEN was administered for at least 7 days at home orally or via nasogastric tube. In a propensity score–matched analysis, those with EEN had lower rates of septic complications and primary stomas. Intra-abdominal infections were significantly lower in the patients receiving EEN (20% vs 42%), and primary stoma creation was also lower in this group.

Li et al. assessed preoperative EEN retrospectively but also sought to evaluate immunosuppressive medication drug–free intervals prior to surgery.[66] Of the 708 surgeries included, 286 (40%) were for obstruction/stricture. Patients receiving peptide-based EEN, delivered by nasogastric feeding, had a slightly higher BMI just prior to surgery compared with other patients. In support of EEN, these patients had lower rates of infectious and noninfectious complications after surgery compared with other groups, after adjustment for other risk factors in a multivariable analysis.

In the smaller study by Wang et al., adult patients receiving EEN were compared with those who had no perioperative nutrition therapy. The authors stated that the primary indication for surgery was "fibrous stenosis," suggesting that patients with stricturing disease constituted most patients. Patients in the EEN group had a peptide-based feed via nasogastric tube for 4 weeks prior to surgery.[67] They found that both infections and noninfectious postoperative complications were significantly less common in the patients receiving EEN.

A special concern for patients with stricturing disease is whether they may develop obstructive symptoms that limit the amount of enteral volume tolerated. Heerasing et al. administered EEN orally and found that 3 of 51 patients (6%) could not tolerate the full course.[64] In the aforementioned study from Zhu et al., 5 of 91 patients (5%) required PN, suggesting that EEN is relatively well tolerated in this population.[74] Abdalla et al. noted 20 of 149 patients (20%) required PN to supplement EEN, with statistically similar rates of PN use in those with and without strictures.[65] Meade et al. noted EEN intolerance in 39 of 181 patients (19%) and, on multivariable analysis, found prestenotic dilation was not a risk factor for intolerance.[68]

In summary, patients with stricturing disease appear able to tolerate preoperative EEN, and although studies do not isolate this group separately, they suggest that EEN decreases the risk of postoperative complications. Given the concern for inability to tolerate EEN in patients with a partial small bowel obstruction, further study is warranted and should consider decisions about elemental vs polymeric feeds, planned combination with PN, and oral vs nasogastric tube administration of EEN.

Fistulizing disease

The three prior studies from Heerasing et al., Meade et al., and Li et al. additionally included patients with fistulizing disease, constituting nearly 50% of the patients in these populations. In the studies from Heerasing et al. and Meade et al., there were significantly decreased rates of postoperative complications for all patients, as previously mentioned, although no subgroup analysis was performed in the fistulizing group.[64,68] In the retrospective study from Li et al. assessing immunosuppressive medication drug–free intervals prior to surgery, nearly 50% of the group receiving EEN had a history of fistulizing disease, and 30% had demonstrated fistulas on the operative report.[66] Subgroup analysis was not specifically performed, but again, those receiving EEN demonstrated lower rates of

infectious and noninfectious complications after surgery on multivariable analysis.

Other studies previously discussed in the stricturing section also included data for patients with fistulizing disease. In the small series by Yamamoto et al., 42% of patients had penetrating disease.[76] Although the study showed an overall benefit of elemental EEN prior to surgery, penetrating disease was associated with more septic complications and complications overall on multivariable analysis. In the analysis of patients enrolled in the GETAID study from Abdalla et al., 67 of 149 (45%) of patients had fistulizing CD prior to surgery. In the group at large, preoperative EN was associated with fewer intra-abdominal septic complications; however, patients with perforating CD and those with internal fistulas were at higher risk of EN failure, defined as the need to switch to preoperative PN.[65]

Li et al. evaluated EEN and postoperative results in 123 patients with CD and enterocutaneous fistulas.[72] None of these patients had preoperative infliximab, owing to unavailability of this medication at the time. Patients receiving EEN ($n = 55$) had a 3-month course with a peptide-based formula via nasogastric tube and were compared with 68 who did not. Those receiving EEN were noted to have higher BMI prior to surgery, although CDAI scores were similar between the groups. CRP decreased in both groups but more markedly in those receiving EEN, and they also had lower CRP values at time of surgery. Intra-abdominal postoperative septic complications occurred less frequently in the group receiving EEN (4% vs 18%).

The concern for poor tolerance of EEN appears to be just as valid in patients with fistulizing disease, with Abdalla et al. showing an increased risk of requiring PN in these patients.[65] On the other hand, in the study by Meade et al., patients with a penetrating phenotype were not less likely to tolerate EN per protocol for ≥2 weeks.[68] In the study by Li et al., the authors noted they were not able to collect data about the behavior of the enterocutaneous fistula output, challenges with pouching, or fistula control in the EEN group.[72]

Although there may be some benefit from EEN in the setting of fistulizing disease as evidenced by the literature, additional evidence suggests that those with fistulizing disease are more likely to develop postoperative infections as well as PN requirement. However, there are overall mixed data regarding the risk of postoperative intra-abdominal infections, and it is difficult to make definitive conclusions. Additionally, those with fistulizing disease seem less likely to tolerate EEN. Similar to stricturing disease, further study on optimal type of feed and use of PN as an adjunct may be useful given the risk of poor tolerance.

PREOPERATIVE PN

Preoperative PN has been shown to not increase postoperative complications, and several studies have actually demonstrated reduced risk of postoperative complications (Table 4).[77–79] A randomized controlled trial from 2005 assessing PN in malnourished CD patients, defined by BMI <15.0, found that postoperative complications were similar between those who did and did not receive PN, although BMI improved and the rate of return to work was higher in the PN group.[80] It is important to note that preoperative PN is associated with increased risk for catheter-associated infections.[81] Although prior research has evaluated use of PN in the preoperative period for all patients with CD, preoperative data specific to stricturing and fistulizing disease are limited.

Stricturing disease

Ayoub et al. attempted to highlight the stricturing phenotype of CD in a 2019 retrospective cohort study on preoperative PN.[69] They compared 55 adult patients who had received preoperative PN prior to surgery for CD with 89 patients who did not; 58% of patients receiving preoperative PN had this for >60 days. Of note, 37% patients had stricturing disease, and this group was rather high risk compared with other cohorts in the EEN studies, with 58% of patients requiring colon resection, 76% receiving biologics within 8 weeks prior to surgery. In an unadjusted analysis, patients receiving PN did not have a higher risk of postoperative complications, and in a multivariable analysis, patients receiving PN had lower odds of noninfectious complications.

Another retrospective observational study of 186 adult patients with CD (59.7% with stricturing disease) evaluated the impact of ω-3 fatty acid–based injectable lipid emulsion (ILE) supplementation on reducing postoperative complications.[70] Patients were placed in two groups dependent on whether supplemental ω-3 fatty acid–based ILEs were provided. Both groups received baseline medium-chain and long-chain lipid emulsions with a lipid formulation of 64% soybean oil and 36% medium-chain triglyceride oil, but one group received additional supplemental ω-3 fatty acid–based ILE. The supplemental dosing for the ω-3 fatty acid–based ILEs was at 0.2 mg/kg/day. The 83 adult patients who received ω-3 fatty acid–based ILEs after surgery had a lower CRP level on postoperative day 3 and shorter length of stay with the hospitalization.

Surprisingly, further studies on preoperative PN in stricturing disease are not available. Because of the risks

of PN, including line infections and deep vein thromboses, preoperative EEN should be favored as the initial route.[71]

Fistulizing disease

The role of PN in the perioperative period for fistulizing disease is additionally poorly defined. As noted above, current practice is to attempt preoperative EEN given the potential risks of PN. In a feasibility study, Zerbib et al. developed a preoperative protocol including bowel rest, nutrition therapy, and weaning of immunosuppressive medications prior to surgery in adult patients undergoing ileocolic resection for fistulizing CD. The authors attempted to give EEN to all patients initially, but 58% required PN because of aggravation of symptoms. The study demonstrated that with this protocol, postoperative morbidity was 18%, and there was no mortality. Although this was a noncontrolled study, it demonstrated that PN could have a role in preoperative nutrition optimization.[73]

CONCLUSION

Our review highlights various potential benefits of various modalities of nutrition in stricturing and fistulizing CD. Existing data suggest that EEN and PEN may have benefit as a treatment modality in both stricturing and fistulizing CD, although EEN is likely more beneficial for stricturing disease. In the perioperative period, evidence suggests that preoperative EEN not only is well tolerated but also decreases the risk of postoperative complications in stricturing disease. The data remain more mixed for EEN in fistulizing CD given the potential for postoperative infection. Despite these advantages, the evidence remains limited, and research is required to better understand the role, formulation, and duration of oral diet, EEN, and PN in these CD phenotypes. Higher-quality evidence, such as randomized controlled trials, is also required to improve the quality of evidence. Furthermore, there is limited information for the utility of EEN as an adjunct therapy for stricturing or fistulizing CD that is more difficult to control. For perioperative considerations, further research into the effects of delaying surgical management for preoperative EEN is needed, along with further insight into the role of PEN prior to surgery. Moving forward, it is critical that studies address these questions to optimize the role of nutrition in stricturing and fistulizing CD.

AUTHOR CONTRIBUTIONS

Kush Fansiwala, Neha D. Shah, Kelly A. McNulty, Mary R. Kwaan, and Berkeley N. Limketkai equally contributed to the conception and design of the research, drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Neha D. Shah is a consultant for GI onDEMAND with the American College of Gastroenterology and Gastro Girl. Kush Fansiwala, Kelly A. McNulty, Mary R. Kwaan, Berkeley N. Limketkai declare no conflict of interest.

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