Benefits of Exclusive Enteral Nutrition in Adults With Complex Active Crohn's Disease: A Case Series of 13 Consecutive Patients

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Background and Aims: Immunosuppressive therapy is routine for adults with complex active Crohn's disease (CD), however carries risks, particularly in the setting of sepsis. Exclusive enteral nutrition (EEN) is widely used in paediatric CD, yet efficacy data in adults are sparse. This study evaluated outcomes of EEN in adults with complex active CD.

Methods: Between December 2016 and June 2018, 13 patients with complex active CD (range 20–74 years) managed at a single hospital received 2 or more weeks of EEN. Patients were offered EEN based on either malnutrition, contraindication to immunosuppression, or CD refractory to multiple therapies. Subjective and objective outcomes were recorded at 2 and 6 weeks and compared with baseline data.

Results: Nine of 13 patients experienced subjective improvement in wellbeing. Objective improvements included nine CRP decrements (median = 87.7 mg/L, IQR = 70.6 mg/L), nine serum albumin increments (median = 7 g/L, IQR = 4 g/L), and six gained weight (median = 3.6 kg, IQR = 3.0 kg). All five patients with complex abscess resolved without surgery. One ileocolic fistula and one enterocutaneous fistula achieved resolution without surgery. One of two perianal fistulae cases resolved without surgery. Seven of 10 patients initially thought to need surgery avoided it due to disease resolution. Only one of the three patients who proceeded to surgery sustained a post-operative complication. There were no EEN-associated complications.

Conclusions: In complex active CD, our real-world data show that EEN improves wellbeing, decreases inflammatory markers, leads to healthy weight gain, reduces need for surgical intervention, and reduces postoperative complications.

Key Words: inflammatory bowel disease, Crohn's disease, exclusive enteral nutrition

INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory disease of the gastrointestinal tract that is characterized by fever, abdominal pain, diarrhea, blood, and/or mucus in stool.[1] Despite newer biological agents, corticosteroids are still frequently used as first line therapy in acutely unwell adult patients with active CD. However, corticosteroids do not induce mucosal healing and carry a myriad of side effects including glucose intolerance, sleep disturbances, mood changes, cushingoid features, and increase risk of sepsis and opportunistic infections.[2] Hence, alternative therapies with fewer side effects are desirable.

Exclusive enteral nutrition (EEN) is an established first line treatment in paediatric CD.[3] EEN involves providing all of a patient's nutritional requirement via a liquid formula, typically for 6 to 8 weeks.[4] A 2007 meta-analysis showed that EEN was inferior to corticosteroid therapy in inducing remission of active adult CD.[5] However, these older studies did not consistently use objective measurements such as biomarkers or mucosal healing to document remission status. Additionally, more recent data on EEN have demonstrated benefits of mucosal healing,[6] healthy weight gain,[7] improved vitamin D levels,[8] improved bone health,[9] and better quality of life.[10] More recent data have shown that EEN may be effective in resolving enterocutaneous fistulae and inflammatory strictures, hence, avoiding need for surgery.[11–13] EEN is recommended as first line

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therapy for active adult CD by the 2018 Japanese Ministry of Health, Labour and Welfare guidelines and this could be partly attributed to EEN's safer side effect profile and higher rates of remission compared with corticosteroids in Japanese data.[14,15]

There has been encouraging data supporting the use of EEN in paediatric patients with active CD.[16,17] The basic premise of efficacy also applies to the adult CD cohort; however, there are limited data examining EEN in the management of adults with CD in Western populations. Reasons cited for poor replication of positive data in Western adults include unpalatable elemental formulas, anticipated poor compliance, greater clinician acceptance of corticosteroid use in adults when compared with children with CD, and clinician biasness in terms of the choice of treatment. This bias has resulted in a wide variability in use of EEN even in paediatric active CD patients where 62% of European gastroenterologists employ EEN as first line therapy when compared with 4% of North American gastroenterologists.[18,19] Additionally, the perceived poor tolerance of EEN may be a result of clinician biasness as recent studies have actually shown good adherence rates.[20,21] There is an emerging awareness of the potential role for EEN in adults with CD in settings where standard therapy with corticosteroids or other immunosuppressants is contraindicated. Scenarios where EEN appear likely to be beneficial include where there is sepsis, malnutrition, or significant drug side effects. At the Royal Adelaide Hospital around 2016, we initiated more proactive EEN use as main therapy in adult patients with active and complex CD. In this case series, we report our experience to date.[21]

METHODS

A retrospective analysis of the Royal Adelaide Hospital IBD database was undertaken. This database has been prospectively maintained since early 2008 within the Department of Gastroenterology. All admitted patients with active CD who were offered EEN between December 2016 and June 2018 and tolerated this treatment for a minimum of 2 weeks were included. Patients with CD were selected to receive EEN by gastroenterologists and with discussion at a fortnightly IBD multidisciplinary team (MDT) meeting which also consisted of colorectal surgeons, IBD nurse specialists, radiologists, psychologists, and dietitians. To minimize selection bias, EEN use was actively considered and positively promoted as a standard option during the IBD MDT. Generally, use was recommended based on either malnutrition, contraindication to immunosuppression (usually sepsis) or CD refractory to multiple drugs (Fig. 1).

Dietitians were involved in all cases and they assisted in evaluating patient's nutritional status, estimate caloric and protein requirements, determine EEN prescription, implementation and management of EEN, review tolerance and compliance of EEN, and support reintroduction of diet post EEN. Patient's calorie requirements were estimated using 105–126 kJ/kg body weight and protein requirements at 1.2–1.5 g/kg body weight. A 25% adjusted body weight was used for obese patients and weight gain factor or kilojoule requirements up to 145 kJ/kg

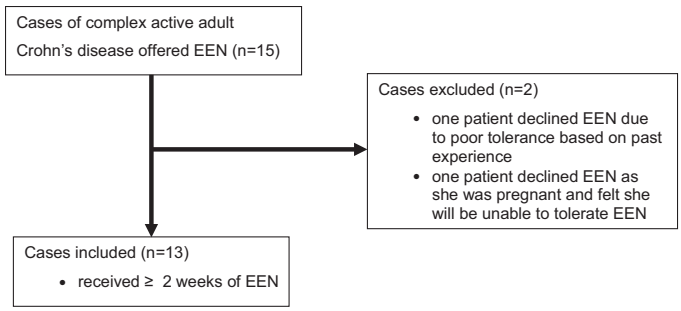

FIG. 1. Inclusion and exclusion of patients.

body weight for those that were malnourished. Malnutrition was defined by Patient Generated-Subjective Global Assessment (PG-SGA) score B and C or Body Mass Index (BMI < 18 kg/m^2) or unintentional weight loss >10% in the last 3–6 months or a combination of unintentional weight loss >5% in 3–6 months and BMI <20kg/m^2. Based on diet history at baseline assessment, those at risk of vitamin and mineral deficiency were screened and supplemented if deficient. All patient were 100% exclusively fed EEN by mouth. Water and clear broth were allowed during the period of EEN per protocol. The EEN formula used was Fortisip by Nutricia Advanced Medical Nutrition, a polymeric 1.5 cal/ml, low lactose, low residue, oral nutrition supplement drink.

Patient age, sex, date of diagnosis, Montreal classification, prior treatment, treatment given alongside EEN, indication for EEN, duration of EEN, and tolerability were examined. Date of diagnosis of CD was defined as date of first histological confirmation. Patents' data were reviewed at 2 and 6 weeks to record both subjective and objective outcomes compared with baseline. Subjective outcomes included general well-being, physical activity, stool frequency, and abdominal pain. Subjective outcomes were recorded from patient history during inpatient ward rounds, or outpatient clinic, or telephone follow-ups. Improvement in wellbeing was considered if any of the following was reported: ability to return to activities of daily living, increase physical activity or reduction in symptoms such as abdominal pain or stool frequency. Objective outcomes included weight (kg), serum albumin (g/L), serum C-reactive protein (CRP) (mg/L), CT scan and MR enterography findings, the need for surgery, and postoperative outcomes in patients who underwent surgery. Data were expressed either as median with interquartile range (IQR).

RESULTS

Demographics and Tolerance of EEN

Between December 2016 and June 2018, 13 adult inpatients with active Crohn's disease were recommended to receive EEN at the Royal Adelaide Hospital. This included seven males and six females, age ranging from 20 to 74 years (median = 41, IQR = 16.3). Of the 13 patients, two patients received

the minimal of 2 weeks of EEN meeting the inclusion criteria (median duration = 6). The reasons being poor tolerability (n = 1) and cessation postoperatively (n = 1). The remaining 11 patients received 5 weeks or more of EEN, and this was reported to be well tolerated by all of them. This translates to an actual tolerance rate of 92% (12/13; 95% CI [0.172, 0.474]) (Table 1).

Indications for EEN

Small bowel obstruction—Cases 1 and 2

Cases 1 and 2 were admitted with malnutrition and small bowel obstruction (SBO) secondary to active CD. Their SBOs were managed conservatively with 1-week course of corticosteroid. EEN was commenced once SBO resolved. Case 1 avoided surgery as she achieved clinical CD remission with a drop in CRP (from 29 to 1.9 mg/L). Whilst Case 2 required bowel resection for active CD 4 weeks after EEN was initiated, her albumin level increased (from 26 to 28 g/L). She did not experience any postoperative complication. Both cases tolerated EEN well and reported subjective improvement in well-being.

Contraindication to immunosuppression due to complex abscesses—Cases 3 to 6

These four patients had active CD and presented with complex intra-abdominal abscesses, undrainable by interventional radiology. To avoid immunosuppression and surgical intervention, these patients received IV antibiotics and EEN as their only treatment. Only one patient proceeded to have small bowel resection after 7 weeks of EEN when the abscess had resolved. This patient was initially unsuitable for surgery due to severe malnutrition. He was optimized preoperatively with EEN with weight gain (from 78 to 83 kg) and an increase in serum albumin (from 19 to 25 g/L). This patient also avoided any postoperative complications. Cases 4–6 achieved clinical remission on EEN and antibiotics and avoided surgery with resolution of their complex collections as confirmed on CT scans. Cases 5 and 6 also experienced weight gain, increased albumin (from 31 to 34 and 16 to 34 g/L, respectively) and clinically significant decrements in CRP (from 230 to 7.4 and 159.6 to 6.8 mg/L, respectively). Case 4 did not attend follow up, hence, changes for her were not recorded.

Complex abscess and ileocolic fistula—Case 7

This patient was a 41-year-old male with a complex intra-abdominal collection and ileocolic fistula. He was treated with intravenous tazocin and 6 weeks of EEN. CT scan 6 weeks later showed complete resolution of the collection and fistula. In addition to avoiding surgery, his abdominal pain resolved, gained weight, and increased his albumin (from 25 to 32 g/L).

Enterocutaneous fistula—Case 8

This was a 65-year-old female patient who presented with malnutrition and enterocutaneous fistula. She received Azathioprine, budesonide, tazocin, and also 7 weeks of EEN. Case 8's fistula completely resolved without the need for surgery and she also experienced improvements in well-being, physical activity, weight (from 62 to 65 kg), and albumin (from 29 to 33 g/L).

Perianal fistulae—Cases 9 and 10

Cases 9 and 10 were both active CD refractory to multiple drugs and associated with perianal fistula disease. In addition, case 9 developed CD-associated oligoarthritis while an inpatient. Both cases were managed with EEN and a short duration of draining seton. Subjective improvements in well-being and physical activity were reported. Objectively, both of their albumin increased (from 34 to 41 and 28 to 32 g/L, respectively) and CRP decreased (from 112.2 to 16 and 69 to 43 mg/L, respectively). After seton removal, case 9's fistula resolved without further need for operations, and their oligoarthritis also resolved without the need of immunomodulators. Case 10 underwent a left colectomy and proctectomy 2 weeks post-EEN and postoperatively he developed a presacral collection which was managed by CT-guided percutaneous drainage.

Bridging between treatment—Case 11

Case 11 was a 35-year-old male who received 6 weeks of EEN post small bowel resection for active CD while bridging to Azathioprine. He reported subjective improvement in wellbeing and objectively he experienced weight gain (from 75 to 79.6 kg), decrease in CRP (from 2.2 to 0.7 mg/L), and developed no postoperative complication.

Last line therapy—Cases 12 and 13

The majority of patients in this series including cases 12 and 13 had been refractory to and/or intolerant of multiple drugs. Case 12 was a 21-year-old female with malnutrition and extensive small bowel involvement, making her unsuitable for surgery. EEN was employed, but due to poor tolerance, she received only 2 weeks of EEN. Despite this, her abdominal pain resolved, she had decrease in stool frequency and CRP (from 21 to 13 mg/L), and was able to be discharged.

Case 13 was a 27-year-old male who received 6 weeks of EEN whilst awaiting funding approval for vedolizumab. His abdominal pain resolved, and he reported improvements in well-being and physical activity. At the end of 6 weeks of EEN (just before vedolizumab was initiated), he increased his serum albumin (from 29 to 35 g/L) and decreased his CRP (from 98 to 1.4 mg/L).

DISCUSSION

It is estimated that approximately 85,000 Australians are currently affected by IBD and the number is expected to reach 100,000 by 2022.[22] This increased incidence of IBD is mirrored worldwide. Thus, with IBD prevalence steadily increasing, there

TABLE 1. Patient Characteristics

Case	Age	Sex	DD[a]	Montreal Classification	Prior Treatment	Treatment in Conjunction With EEN	Reason for EEN	Duration of EEN (Weeks)	Tolerability	Final Results	
										Subjective Changes	Objective Changes
1	74	F	5	A3, L3, B1	Prednisolone Azathioprine	Hydrocortisone Azathioprine	▪ Active CD resulting in recurrent SBO[b] ▪ Malnutrition	6	Good	▪ ↑well-being	▪ ↓CRP (29 to 1.9) ▪ CD remission ▪ Avoided surgery
2	55	F	12	A2, L3, B3	Hydrocortisone Ustekinumab	Hydrocortisone	▪ Active CD resulting in SBO[b] ▪ Malnutrition	5	Good	▪ ↑ well-being	▪ ↑Albumin (26 to 28) ▪ No post-operative complication (ileocolic resection)
3	50	M	32	A2. L1, B3	Azathioprine	Tazocin	▪ Unable to immunosuppress due to complex collection and recent skin cancer ▪ Extensive Crohn's not suitable for surgery ▪ Malnutrition	6	Good	▪ Abdo pain resolved	▪ ↑Weight (78 to 83) ▪ ↑Albumin (19 to 25) ▪ ↓CRP (96 to 8.3) ▪ Abdominal collection resolved ▪ Reduced extensiveness and preoperative optimisation ▪ No post-operative complication (small bowel resection)
4	27	F	0	A2, L1, B3	None	Metronidazole Ceftriaxone Amoxycillin	▪ First presentation ▪ Unable to immunosuppress due to complex collection	6	Good	▪ Abdo pain resolved	▪ Reduced extensiveness and preoperative optimisation ▪ Abdominal collection resolved ▪ Avoided surgery
5	20	M	0	A2. L1, B3	None	Tazocin	▪ Unable to immunosuppress due to undrainable intra-abdominal collection	7	Good	▪ Abdo pain resolved ▪ ↑ well-being	▪ ↑Weight (93 to 93.4) ▪ ↑Albumin (32 to 43) ▪ ↓CRP (230 to 7.4) ▪ CT showed completed resolution of inflammation and collection ▪ Avoided surgery
6	65	F	0	A3, L1, B1	Amoxicillin Metronidazole Gentamicin CT guided drainage	Amoxicillin Metronidazole Gentamicin	▪ First presentation ▪ Unable to immunosuppress due to recurrent complex abscess	6	Good	▪ Abdo pain resolved ▪ Nausea and vomiting resolved ▪ ↑ well-being	▪ ↑Weight (58 to 62.1) ▪ ↑Albumin (16 to 34) ▪ ↓CRP (159.6 to 6.8) ▪ CT showed resolution of collection ▪ Avoided surgery
7	41	M	10	A2, L1, B1	Azathioprine	Tazocin	▪ Unable to immunosuppress due to complex collection ▪ Ileocolic fistula	6	Good	▪ Abdo pain resolved	▪ ↑Weight (92 to 93) ▪ ↑Albumin (25 to 32) ▪ CT showed resolution of collection and fistulas ▪ Avoided surgery
8	65	F	0	A3, L1, B3	Azathioprine Budesonide	Azathioprine Budesonide Tazocin	▪ Enterocutaneous fistula ▪ Malnutrition	7	Good	▪ ↑ well-being ▪ ↑ Physical activity ▪ ↑ADL[c]	▪ ↑Weight (62 to 65) ▪ ↑Albumin (29 to 33) ▪ Fistula resolved ▪ Avoided surgery
9	27	M	7	A2, L3, B2	Azathioprine Methotrexate Infliximab Vedolizumab Ustekinimab		▪ Refractory and allergic to multiple drug ▪ Multiple anal fistula ▪ Oligoarthritis	6	Good	▪ ↑ well-being ▪ ↑Physical activity	▪ ↑Albumin (34 to 41) ▪ ↓CRP (112.2 to 16) ▪ Oligoarthritis resolved ▪ Avoided surgery

TABLE 1. Continued

Case	Age	Sex	DD[a]	Montreal Classification	Prior Treatment	Treatment in Conjunction With EEN	Reason for EEN	Duration of EEN (Weeks)	Tolerability	Final Results: Subjective Changes	Final Results: Objective Changes
10	31	M	11	A2, L2, B3	Azathioprine Infliximab Mesalazine	Budesonide	▪ Active Crohn's refractory to multiple drug ▪ Anal fistula ▪ Malnutrition	2	Good	▪ ↑ well-being	▪ ↑Albumin (28 to 32) ▪ ↓CRP (69 to 43) ▪ Presacral collection (10days post left colectomy & proctectomy)
11	35	M	0	A2, L1, B2	None	None	▪ Post-operative (small bowel resection) ▪ Bridging to immunotherapy	6	Good	▪ ↑ well-being	▪ ↑Weight (75 to 79.6) ▪ ↓CRP (2.2 to 0.7) ▪ no post-operative complication
12	21	F	8	A1, L3, B2	Azathioprine Methotrexate Infliximab Adalimuab	Azathioprine Adalimuab	▪ Refractory and allergic to multiple drug ▪ Extensive Crohn's not suitable for surgery ▪ Malnutrition	2	Poor	▪ Abdo pain resolved ▪ ↓ Frequency of loose stools	▪ ↓CRP (21 to 13)
13	41	M	27	A2, L3, B2	Azathioprine Infliximab Adalimumab		▪ Crohn's flare ▪ Refractory and allergic to multiple drug ▪ Bridging to Vedolizumab	6	Good	▪ Abdo pain resolved ▪ ↑ well-being ▪ ↑Physical activity	▪ ↑Albumin (29 to 35) ▪ ↓CRP (98 to 1.4)

[a]DD = Crohn's Disease duration (years).
[b]SBO = Small bowel obstruction.
[c]ADL = activity of daily living.

is a compelling need to find and use effective and safe treatment modalities.

Common side effects reported in previous metanalysis included vomiting, diarrhoea, heartburn, and flatulence. [23] In our study, not a single patient experienced any serious side effects from EEN. Nine out of 13 patients (69%) experienced subjective improvement in wellbeing and three patients reported improvements in physical activity while on EEN.

Up to 80% of patients with active CD suffer from malnutrition secondary to malabsorption, decreased intake and increased losses.[24] Six of our patients (46%) experienced weight increments (median = 3.6 kg, IQR = 3.0 kg) of which two of them were deem as having malnutrition during initial assessment. Our study illustrated noticeable improvements in weight, mirroring previous studies.[13, 25] Of the five complex undrainable abscesses, four gained weight (increments ranging between 0.4 and 5 kg) with an increment in albumin (ranging between 5 and 18 g/L). To the best of our knowledge, our paper is the first to demonstrate weight gain with EEN use in patients with complex CD-associated abscesses. We were unable to demonstrate weight gain in case 4 as the patient did not attend subsequent follow-up after discharge.

Preoperative hypoalbuminaemia has been demonstrated to be a marker of systemic inflammation, indicator of prolonged inpatient stay, strong predictor for postoperative morbidity and mortality, and an independent risk factor for all complications.[26,27] In our cohort, nine patients (69%) had an increase in serum albumin (median = 7 g/L, IQR = 4 g/L). It is worth noting Case 9 only received 2 weeks of EEN but nonetheless had an increase in albumin (from 28 to 32 g/L). Albumin and CRP has also been shown to be useful indicator of Crohn's disease activity. [28] Nine of our patients (69%) demonstrated decrease in CRP (median = 87.7 mg/L, IQR = 70.6 mg/L).

Ten of our patients were deemed as possibly requiring surgery in the near term and were being optimized for this. Seven of these patients (70%) underwent remission with EEN and avoided surgery. This is consistent with previous studies which demonstrate a clinically significant number of patients avoiding surgery with preoperative use of EEN. [11, 12] Two of the three patients who proceeded to surgery avoided postoperative complications despite their complex phenotype and unfavorable risk profile. Previous studies estimated reduction in rates of postoperative complications from 95% (without preoperative EEN) to 48% (with preoperative EEN).[25] Malnutrition is a well-established risk factor for postoperative morbidity.[29] This low postoperative morbidity rate seems to correlate with the improved nutritional status and increase serum albumin level. This study suggests that EEN is an easy way to preoperatively optimize a CD patient by improving nutritional status without side effects and potentially reduces postoperative morbidity, and in some cases, avoiding surgery altogether. This in turns reduces cost for patients and health organisations.

Of the four cases with fistula, three fistulas resolved without the need for major surgery (one perianal fistula, one ileocolic fistula, and one enterocutaneous fistula). Previous studies only described EEN use in enterocutaneous fistulas and its associated higher rates of fistula closure and reduced risk of postoperative intraabdominal septic complications.[13,30] However, this is the first case series describing benefit of EEN use in CD-associated perianal fistulas and ileocolic fistulas.

We acknowledge the limitations with case series, such as their retrospective nature, with possible incomplete data recording, confounding with other medications, and the absence of controlled comparison. We also recognize compliance rates could be inaccurate as upon discharge there was no way of enforcing that the patient's diet at home consisted only purely of EEN. We also appreciate that some of the documented albumin increments were small and most did not normalise albumin levels; however, the increments are clinically significant. This is also a single centre study reporting on a small sample size, without sufficient numbers to elicit robust statistical analysis. However, we note that despite clinicians' unwillingness to use it previously and negative patient perceptions, clear benefits in complex high-risk cases appear to have occurred.

In summary, these data may encourage more clinicians to use EEN in adults with CD and formally evaluate its role in clinical practice. Given our encouraging results, a randomized controlled trial against "standard" therapy appears justified. Furthermore, our real-world data strongly suggest that EEN is worthy of more serious consideration as a first line therapy in adults admitted with complex, active CD.

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AUTHORS' CONTRIBUTIONS

Jianliang Liu is the main author who was in charge of the design of the study, acquisition of data, interpretation of the data, drafting the article, and final approval of the final manuscript. Prof. Andrews (Gastroenterologist consultant), A/Prof. Sammour (Colorectal Surgeon), and Dr. Bryant(Gastroenterologist consultant) are the main supervisors who were heavily involved in the conception and design of the study, interpretation of the data, critically revising the article, and approving the final manuscript. Rachel Grafton is our dedicated IBD Clinical Practice Consultant who was heavily involved in the conception and design of the study, acquisition of data, interpretation of the data, critically revising the article, and approving the final manuscript. Eliza Simpson,

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REFERENCES

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet.* 2012;380:1590–1605.
2. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol.* 2006;4:621–630.
3. Ruemmele FM, Veres G, Kolho KL, et al.; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis.* 2014;8:1179–1207.
4. Whitten KE, Rogers P, Ooi CY, Day AS. International survey of enteral nutrition protocols used in children with Crohn's disease. *J Dig Dis.* 2012;13:107–112.
5. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *The Cochrane Database Syst Rev*. 2007(1):CD000542.
6. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol.* 2006;4:744–753.
7. Day AS, Whitten KE, Lemberg DA, et al. Exclusive enteral feeding as primary therapy for Crohn's disease in Australian children and adolescents: a feasible and effective approach. *J Gastroenterol Hepatol.* 2006;21:1609–1614.
8. Levin AD, Wadhera V, Leach ST, et al. Vitamin D deficiency in children with inflammatory bowel disease. *Dig Dis Sci.* 2011;56:830–836.
9. Whitten KE, Leach ST, Bohane TD, et al. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol.* 2010;45:399–405.
10. Afzal NA, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, et al. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment Pharmacol Ther.* 2004;20:167–172.
11. Heerasing N, Thompson B, Hendy P, et al. Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for adults with Crohn's disease. *Aliment Pharmacol Ther.* 2017;45:660–669.
12. Day A, Wood J, Melton S, Bryant R. Exclusive enteral nutrition: An optimal care pathway for use in adult patients with active Crohn's disease. *JGH Open.n/a(n/a)*.
13. Yan D, Ren J, Wang G, et al. Predictors of response to enteral nutrition in abdominal enterocutaneous fistula patients with Crohn's disease. *Eur J Clin Nutr.* 2014;68:959–963.
14. Okada M, Yao T, Yamamoto T, et al. Controlled trial comparing an elemental diet with prednisolone in the treatment of active Crohn's disease. *Hepatogastroenterology.* 1990;37:72–80.
15. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol.* 2018;53:305–353.
16. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr.* 2000;31:8–15.
17. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. *Aliment Pharmacol Ther.* 2007;26:795–806.
18. Levine A, Milo T, Buller H, Markowitz J. Consensus and controversy in the management of pediatric Crohn disease: an international survey. *J Pediatr Gastroenterol Nutr.* 2003;36:464–469.
19. Lawley M, Wu JW, Navas-López VM, et al. Global Variation in Use of Enteral Nutrition for Pediatric Crohn Disease. *J Pediatr Gastroenterol Nutr.* 2018;67:e22–e29.
20. Kansal S, Wagner J, Kirkwood CD, Catto-Smith AG. Enteral nutrition in Crohn's disease: an underused therapy. *Gastroenterol Res Pract.* 2013;2013:482108.
21. Wall CL, Day AS, Gearry RB. Use of exclusive enteral nutrition in adults with Crohn's disease: a review. *World J Gastroenterol.* 2013;19:7652–7660.
22. Crohn's & Colitis Australia. About IBD 31 July 2019. Available from https://crohnsandcolitishub.com.au/about-ibd/.
23. Narula N, Dhillon A, Zhang D, et al. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2018;4:CD000542.
24. Vadan R, Gheorghe LS, Constantinescu A, Gheorghe C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab. *Clin Nutr.* 2011;30:86–91.
25. Wang H, Zuo L, Zhao J, et al. Impact of Preoperative Exclusive Enteral Nutrition on Postoperative Complications and Recurrence After Bowel Resection in Patients with Active Crohn's Disease. *World J Surg.* 2016;40:1993–2000.
26. Patel KV, Darakhshan AA, Griffin N, et al. Patient optimization for surgery relating to Crohn's disease. *Nat Rev Gastroenterol Hepatol.* 2016;13:707–719.
27. Haupt W, Holzheimer RG, Riese J, et al. Association of low preoperative serum albumin concentrations and the acute phase response. *Eur J Surg.* 1999;165:307–313.
28. Qin G, Tu J, Liu L, et al. Serum Albumin and C-Reactive Protein/Albumin Ratio Are Useful Biomarkers of Crohn's Disease Activity. *Med Sci Monit.* 2016;22:4393–4400.
29. Schiesser M, Müller S, Kirchhoff P, et al. Assessment of a novel screening score for nutritional risk in predicting complications in gastro-intestinal surgery. *Clin Nutr.* 2008;27:565–570.
30. Li G, Ren J, Wang G, et al. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. *Eur J Clin Nutr.* 2014;68:441–446.